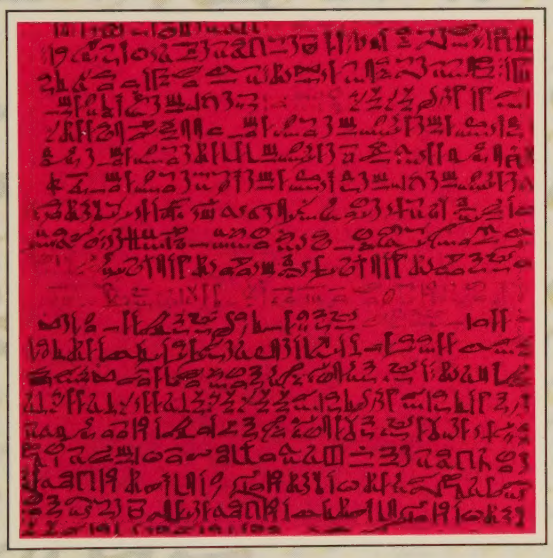
Type 2 Diabetes mellitus

Pathology and treatment



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De promotie vindt plaats in de Aula van het Faculteitsgebouw van de Rijksuniversiteit Limburg, Tongersestraat 53, Maastricht, op vrijdag 24 mei 1991 om 16.00 uur.

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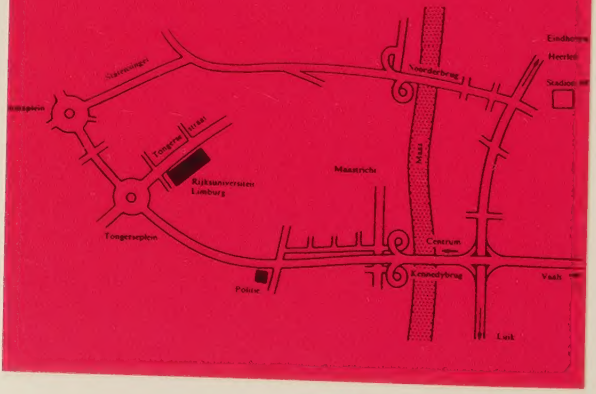

Type 2 diabetes mellitus

Pathology and treatment

Cover:
The *Georg Ebers papyrus*, dating from 1550 B.C., discovered at Thebes in 1872, contains an extensive medical therapeutic text covering many subjects, among them pharmacologic means of treatment. Possible remedies against a disease with excessive urinary output are mentioned.

Type 2 diabetes mellitus

Pathology and treatment

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Rijksuniversiteit Limburg te Maastricht,
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volgens het besluit van het College van Dekanen,
in het openbaar te verdedigen
op vrijdag, 24 mei 1991 om 16.00 uur

door

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STELLINGEN
behorende bij het proefschrift

Type 2 diabetes mellitus
Pathology and treatment

van
Bruce Wolffenbuttel

Maastricht, 24 mei 1991

1. Type 2 diabetes mellitus is meer dan 'een beetje suiker'.

2. Op grond van de C-peptide stijging na glucagon kunnen die type 2 diabetes patiënten worden geidentificeerd, die bij dieet-falen direct met insuline behandeld dienen te worden.
   (dit proefschrift).

3. Het met behulp van medicamenten zo snel mogelijk normaliseren van de glucose-homeostase bij obese patiënten met type 2 diabetes is te prefereren boven langdurige en vaak frustrerende pogingen tot gewichtsreductie.

4. Combinatie therapie van insuline met glibenclamide heeft geen negatieve effecten op het plasma HDL-cholesterol gehalte.
   (dit proefschrift)

5. Intensieve dieet therapie is voor niet-obese type 2 diabeten met matig-ernstige hyperglycemie een zoethoudertje.
   (dit proefschrift)

6. De bepaling van het fructosamine-gehalte van het plasma als maat voor de gemiddelde instelling bij patiënten met diabetes mellitus is goedkoop, doch weinig waardevol.
   (dit proefschrift)

7. Het gemeten plasma gehalte van HDL-cholesterol bij personen met een matig gereguleerde diabetes mellitus type 2 zegt weinig over de kwaliteit van dit partikel.
   Duell PB, et al. Diabetes 1990; 39: 1257-1263; Diabetes 1991; 40: 377-384

8. Het belang van het plasma gehalte van lipoproteïne(a) als onafhankelijke risico-indicator voor het ontwikkelen van hart- en vaatziekten wordt schromelijk onderschat.

9. De begeleiding van type 2 diabetes patiënten dient een gezamenlijke activiteit van huisarts en internist te zijn.

10. Bij een electieve ingreep als een pancreas-transplantatie dient bij de donor CMV-serologie te worden uitgevoerd.

11. Somatostatine-receptor imaging is een waardevolle aanwinst voor het aantonen van (metastasen van) een endociene tumor.
Lamberts SWJ, et al. New Engl J Med 1990; 323: 1246-1249.

12. Uit thrombocyten afkomstige groeifactoren spelen een belangrijke rol bij de geaccelereerde atherosclerose.

13. Het (politieke) rumoer en gekrakeel rond de aanleg van de Oost-West baan op het vliegveld Beek benadert nog bij lange na niet de nachtelijke geluidsniveau's van de landende en vertrekkende vliegtuigen.

14. De inpandige bergingsruimten, die in het huidige Academisch Ziekenhuis zijn aangewezen als werkkamer voor de medische specialisten, tonen ondubbelzinnig de minachting van bouwkundigen voor het begrip arbeidsomstandigheden.

15. Nog even en er zijn meer antihypertensiva dan hypertensie-lijders.

16. Gebakken lucht ligt meestal zwaar op de maag.

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Some things turn out all wrong,
and some things turn out all right,
Some things don't turn out at all,
but then again they might.

J. Walsh, 1981.

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Scope of this thesis

In the studies that are described in this thesis we tried to answer a number of questions which are related to the management of the patient with type 2 diabetes mellitus in everyday practice, either by the family physician or by the endocrinologist/diabetologist. A central question in this case is by which way we can aim to achieve as-near-as-normal blood glucose levels in (elderly) patients with type 2 diabetes, in order to improve quality of life and reduce the risk for the development of late micro- and macrovascular complications and neuropathy.

The specific problems that are studied within the scope of this thesis are:

1. The frequency by which secondary complications develop in patients with type 2 diabetes, and the consequences of these complications for the daily life of the patient (Chapter 2).
   A more specific question in this respect is which clinical conditions predispose for admission of patients to a nursing home (Chapter 3).
2. The severity of vascular complications and quality of blood glucose control of a certain subgroup of patients, namely those who are chronically admitted to a nursing home; their metabolic control and degree and extent of complications is compared with a group of ambulatory diabetic patients (Chapter 3).
3. The metabolic parameters that should be monitored for the everyday control of type 2 diabetic patients. In more detail it is explored whether the determination of fasting blood glucose levels, as advocated by the Dutch Society for General Practice, is sufficient to ensure adequate follow-up of metabolic control, or whether others measures (blood glucose profiles, glycosylated haemoglobin, fructosamine) are necessary (Chapter 4).
4. The effects of intensified dietary therapy on glucose and lipid metabolism and residual islet B-cell function in obese and non-obese ambulatory patients with recent-onset or longer duration of diabetes (Chapter 5).
5. The best mode of treatment for type 2 diabetic patients, who are unsufficiently controlled by diet alone. Should we then -as is common practice at the moment- start oral hypoglycaemic agents, or is insulin therapy a more rational choice for such patients (Chapter 6).

6. When insulin therapy is instituted, which insulin regimen should be used? Is a combination of oral agents and insulin a feasible and safe approach, and is this scheme preferred above treatment with insulin alone? What are the advantages and disadvantages of the combined therapy regarding lipid metabolism, incidence of hypoglycaemias, and costs of the treatment (Chapters 7 and 8).
7. The psychological and social factors that may be of influence when a patient is transferred from treatment with oral agents to insulin therapy (Chapter 9).

In Chapter 1 aspects of pathophysiology and treatment of type 2 diabetes are reviewed.

CHAPTER 1

Type 2 diabetes mellitus

Pathophysiology and treatment

SUMMARY

Non-insulin-dependent or type 2 diabetes mellitus is a heterogeneous disorder, characterized by impaired insulin secretion by the islet B-cells, diminished peripheral insulin action, and increased hepatic glucose production. The major therapeutic goals in type 2 diabetic patients are to optimize blood glucose control, to reduce overweight and to normalize lipid disturbances and elevated blood pressure, in order to improve the well-being of the patient and reduce the risk for the development of late diabetic complications. Exercise and diet, aiming at weight reduction are the cornerstones of therapy. However, often pharmacologic treatment is necessary, in which case sulphonylurea, metformin or insulin may be employed

INTRODUCTION

The main hormone regulating glucose homeostasis is insulin. This hormone is produced by the B-cells of the islets of Langerhans in the pancreas. An increase in the blood glucose level, for instance after a meal, leads to a stimulation of insulin release. Insulin exerts its glucose-regulating action by stimulating glucose uptake in muscle and fat tissue and by suppressing the glucose production in the liver after binding to a specific receptor in the cell membrane. Further, insulin's action comprises the stimulation of lipogenesis and inhibition of lipolysis, and it increases net protein synthesis by enhancing the use of amino-acids, by stimulation of DNA and RNA synthesis, and by inhibition of protein catabolism (1).

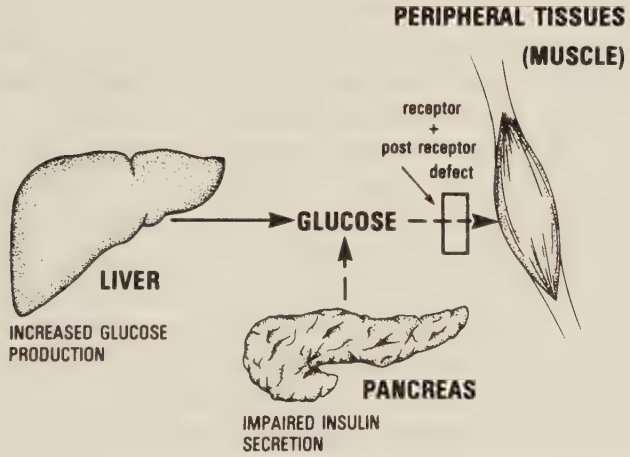

Figure 1. Organ sites involved in the regulation of blood glucose levels. From: Olefsky JM, et al. Am J Med 1988; 85 (suppl 5A): 86-105.

Diabetes mellitus is defined by the WHO (2) as a chronic elevation of the concentration of blood glucose, which characteristically poses a long-term risk to the patient of developing progressive disease of the retina and kidney, damage to peripheral nerves, and aggravated atherosclerotic disease of the heart, legs, and brain. Hyperglycaemia can be caused by a decreased production or by an impaired action of insulin or both (3,4). There are several other hormonal and neural influences that can modulate glucose homeostasis, for instance cortisol and glucagon.

Diabetes was originally considered as a state of insulin deficiency, but the last 25 years the concepts about the disease have changed. In fact, many diabetic patients do secrete insulin. Diabetes can be distinguished in the lean, ketosis-

Table 1. Characteristics of type 1 and type 2 diabetes.

Characteristic	Type 1	Type 2
Weight at diagnosis	non-obese	80% obese, 20% non-obese
Age at diagnosis	usually < 30 years	usually > 40 years
Peak age	12-14 years	65 years
Sex	slight male predominance	female predominance
Incidence	$11/10^5$ (< 20 years)	?
Seasonal variation	present	? absent
Prevalence	0.2-0.5%	? > 2%
Onset	rapid-gradual symptoms severe	mild; insidious incidental finding
Ketosis	usual	uncommon
Remission	often occurs temporarily	? absent
Duration at onset of late complications	after several years	may be present at diagnosis
Islet-cell antibodies	present in 70-95% of cases at diagnosis; may preceed development of disease for more than 9 years	usually absent
Pathology islet Langerhans	inflammatory lesions and progressive loss B-cells	amyloid deposition (40%)
HLA-association	DR-3, DR-4 or both	no
Coincidence with other auto-immune diseases	in 5-10% of all cases	
Familial occurrence		strong hereditary component
Treatment	insulin absolutely necessary	diet & oral hypogl. agents may require insulin

prone, juvenile-onset type (insulin-dependent or type 1, IDDM) and the obese, non-ketosis-prone, maturity-onset form (non-insulin-dependent or type 2, NIDDM) (2). Principle differences between these two types of diabetes mellitus are listed in table 1.

AETIOLOGY AND PATHOGENESIS OF TYPE 2 DIABETES

Type 2 diabetes is a heterogeneous disorder, characterized by defects in insulin secretion as well as insulin action (5). Subjects with modest hyperglycaemia have basal and stimulated insulin levels that are normal or often even increased (6). In patients with more severe hyperglycaemia, absolute insulin levels appear to be normal, but they are inappropriately low in relation to the prevailing blood glucose concentration (7). Insulin response after stimulation with glucose or other secretagogues is normal or increased with modest hyperglycaemia, but severely impaired when glucose levels exceed 11 mmol/l. There exists a defective recognition of glucose signals by the B-cells ("desensitization"), which is suggested to be secondary to hyperglycaemia, and partially restored by normalization of glucose levels (7). Insulin action is impaired: in the basal state this insulin resistance is most pronounced at the level of the liver, the consequent overproduction of glucose primarily causing fasting hyperglycaemia (8). In the post-absorptive state insulin resistance at the level of the peripheral tissues (5), together with the apparent inability to suppress hepatic glucose production (9), and defects in insulin secretion, are responsible for the excessive rise of blood glucose. Although a small decrease in insulin receptor number has been demonstrated (10), the major defect of insulin action is situated at the postreceptor level (11). Impaired glucose uptake, and disturbances of glucose conversion to glycogen (glycogen synthetase) and -to a lesser extent- glucose oxidation (pyruvate dehydrogenase) are the main features (12,13).

ISLET B-CELL DYSFUNCTION AS THE PRIMARY DEFECT?

As mentioned before, glucose is the most important regulator of insulin secretion. A rise of blood glucose level is rapidly sensed by the pancreatic B-cells. It is assumed that the enzyme glucokinase (ATP-D-glucose-6-phosphotransferase) acts as 'glucose sensor' of the B-cell (14). This enzyme determines the metabolic flux through the Embden-Meyerhof glycolysis pathway. It is hypothesized that abnormalities in the regulation of the biosynthesis or degradation

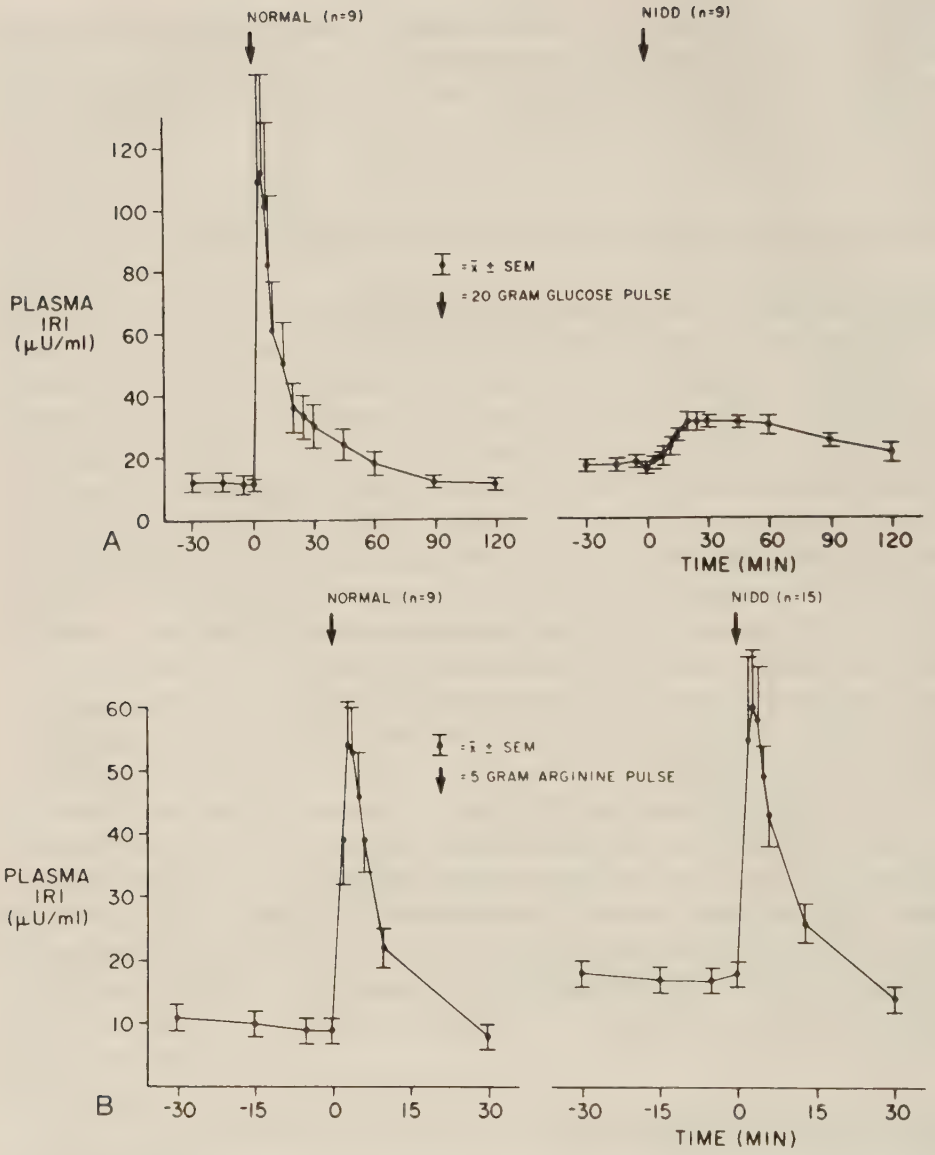

Figure 2. Insulin secretion in type 2 diabetes: A. after iv glucose; B. after iv arginine. From: Pfeifer MA, Halter JB, Porte D Jr. Am J Med 1981; 70: 579-588.

of glucokinase in the beta-cells are involved in the pathogenesis of insulin secretion disturbances in type 2 diabetes (15).

The abnormalities of insulin secretion in patients with type 2 diabetes can be characterized by the following features:

1. normal or elevated basal plasma insulin levels (4-6,16,17);
2. absence or reduction of first phase insulin secretion following glucose (4,18, 19) (figure 2A);
3. diminished second phase insulin secretion (18,20);
4. 'normal' secretory reaction following non-glucose stimuli, as arginine or glucagon (8,19,20) (figure 2B);
5. diminished responsiveness to the potentiating effect of glucose (20,21);
6. changes in oscillatory secretion of insulin (22,23).

In the fasting state, levels of plasma insulin and C-peptide in type 2 diabetic individuals have been reported to be lower, equal to, or higher than in control subjects (16,17). These differences can be accounted for by several factors, such as differences in age, race and body weight of the subjects who were studied, their level of fasting blood glucose, and the specific (radio-immuno)assay used for the determination (17).

When blood glucose levels are elevated, acute insulin response to intravenous glucose is impaired (8,19,24). The response to other secretagogues as intravenous isoproterenol, arginine, or glucagon appears to be near-normal (4). It must be stressed that most responses in the diabetic patients are measured at elevated blood glucose levels, and it has been demonstrated that the response of the B-cells depends on the prevailing blood glucose (24-26). When the blood glucose of non-diabetic subjects is raised to levels similar to those in diabetic patients the release of insulin is greatly enhanced (20). The insulin response to a maximal potentiating glucose level was 5 times higher in healthy control subjects in comparison with diabetic patients. The glucose level at which half maximal potentiation of the insulin response is reached is identical in both groups. This means that the islets in the patient with type 2 diabetes are not totally 'blind' to glucose, but that -in addition to a change in islet sensitivity- islet responsiveness is greatly diminished. However, when insulin instead of C-peptide measurements are used, this approach may result in an overestimation of B-cell responsiveness, as saturation of the hepatic insulin receptors may lead to reduced insulin clearance and peripheral hyperinsulinaemia (25).

Pulsatility of insulin secretion

Pulsatile hormone secretion is found in several endocrine feedback loop systems. Regular pulsatory insulin release is metabolically more efficient in maintaining normal blood glucose levels than non-pulsatory secretion (22). These oscillations are sollicited by an intrapancreatic 'pacemaker' that probably is influenced by the vagus nerve (27). In healthy persons insulin is secreted in regular pulses every 12-15 minutes (23). Pulsatile secretion of insulin is already

decreased in mildly glucose-intolerant subjects who have a family history of type 2 diabetes, despite the fact that first phase insulin secretion is normal in these persons (23). Such persons are at high risk for developing type 2 diabetes, and this implies that loss of pulsatile secretion may be the earliest detectable abnormality of insulin secretion in this disease, either as a specific early defect or as a disturbance caused by minimally elevated blood glucose levels. In patients with established type 2 diabetes, regular oscillatory insulin secretion is lacking, and insulin is characteristically secreted in an irregular fashion (28). Others have not found differences in number of pulses, although the pulses appeared to be less regular and exhibited lower amplitudes (22).

Histology of the pancreas in type 2 diabetes

The observed pathologic changes in the pancreas of type 2 diabetic patients are very variable. A slight reduction in the number of B-cells may be demonstrated (29). The same reduction already can be seen in many elderly healthy persons. Already in 1901, deposits of a hyaline substance have been demonstrated within the islets of Langerhans of diabetic patients (30). This material was later identified as amyloid. Recent studies, however, revealed that the peptide structure differs from systemic amyloid peptides. Thus, the term Islet Amyloid Poly Peptide (IAPP) was introduced (31). It is a 37 amino acid peptide, which shows a 46% homology with calcitonin-gene-related peptide, a hormone formed in the C-cells of the thyroid by alternate DNA processing of the calcitonin gene.

Considerable variation in the occurrence of islet amyloid in type 2 diabetic patients has been reported, with a prevalence as determined from examination of post-morten material varying from 25 to 92% (for review see 32,33). In a recent study in Pima Indians, deposition of IAPP could be demonstrated in pancreatic islets of 77% of diabetic persons, while this was found in less than 10% of non-diabetic individuals (34). No relation could be found between the occurrence of amyloid deposits and body mass index, fasting blood glucose level or age.

Histologically, the amyloid is seen between the islet capillaries and the endocrine cells. The fibrils lie in invaginations of the plasma membranes. IAPP probably originates from the insulin-producing beta-cells. Its presence was also demonstrated inside the beta-cells of both diabetic and non-diabetic subjects. Its physiological role is far from clear. Both involvement in the intracellular processing of insulin, regulation of enzymatic activity and paracrine modulation of insulin secretion have been suggested as main action of the peptide (32). Its co-secretion with insulin and possible vasodilating effects (like CGRP) may increase islet blood flow during insulin secretion (35). However, direct para-

crine inhibition of insulin secretion might be a more direct effect. In addition, modulation of insulin action, and production of insulin resistance by IAPP have been shown *in vitro*, as well as *in vivo* in the rat (36).

Until now it is not known whether the formation of islet amyloid precedes the onset of glucose intolerance and diabetes, or whether it is formed secondarily after the onset of the disease, either directly released or linked to increased insulin biosynthesis. It seems plausible to state, however, that accumulation of amyloid over many years can lead to slowly progressive disruption of the islet architecture and possibly to the abnormalities in the secretion of insulin, as found in type 2 diabetic patients (37).

INSULIN RESISTANCE AS THE PRIMARY LESION?

Insulin resistance is a characteristic feature of type 2 diabetes. It is due to abnormalities in insulin action at the level of the target tissues, resulting in decreased glucose uptake by these tissues. It can be a consequence of receptor or postreceptor defects (3,5,9,11,38-41). Until now it is unknown whether the defects in insulin action precede the onset of the disease and can be regarded as causative factors, or whether these are the consequence of the diabetic state and arise secondary to the exposure to elevated blood glucose levels (39,42).

The insulin receptor (figure 3) consists of two identical alpha-subunits, which are situated extracellular, and two beta-subunits, which have an extracellular, a transmembrane, and a cytoplasmic domain (1,43). The alpha-subunit contains

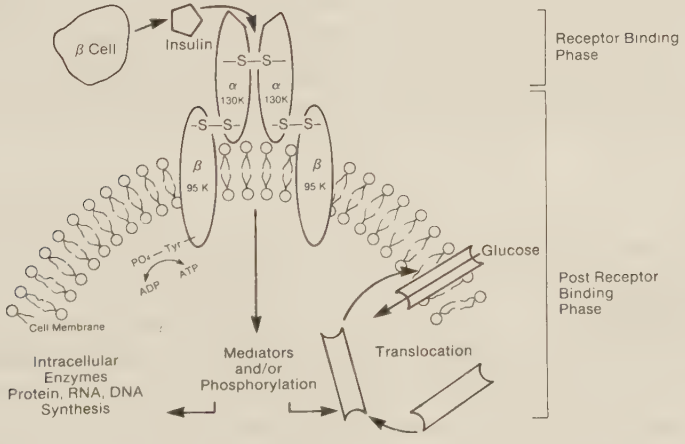

Figure 3. The insulin receptor. From: Olefsky JM, *et al.* Am J Med 1988; 85 (suppl 5A): 86-105.

the insulin binding site. Insulin binding generates a transmembrane signal, that sollicits a chain of intracellular events, such as activation of the receptor tyrosine-kinase, enhanced transport of glucose across the cell membrane, and initiation of a series of phosphorylation-dephosphorylation reactions, eventually leading to stimulation of certain anabolic pathways through activation of specific enzymes (1,44,45).

After transduction of the signal, specific tyrosine residues in the beta-subunit will undergo autophosphorylation. The activated receptor stimulates through an unresolved mechanism the activity of phospholipase C, which is capable to hydrolyse specific glycosyl-phosphoinositides localized in the plasma membrane. The generation of phospho-inositolglycan and diacylglycerol causes selective stimulation of protein phosphatases, which dephosphorylate and thereby activate or inactivate intracellular enzymes involved in carbohydrate metabolism (46).

Based on our knowledge of normal insulin action the effects of receptor versus postreceptor defects on the insulin dose-response curve can be predicted (figure 4). A decrease in the number of insulin receptors or their biological function leads to a rightward shift in the insulin dose-response curve, whereas there is no change in maximal insulin action; this is called a decrease in insulin sensitivity. A pure postreceptor defect in insulin action affects the translation of the insulin signal into intracellular metabolic changes. This will lead to a reduction in biological effects at all insulin concentrations; this situation is termed a decrease in insulin responsiveness (47).

The dose-response curve of *in vivo* insulin action is often assessed with the so-called multiple euglycaemic glucose clamp (48). Similar studies can be performed *in vitro* with isolated adipocytes, monocytes or fibroblasts. In patients with type 2 diabetes the dose-response curve exhibits a rightward shift as well as a marked decrease in the maximal rate of glucose disposal. Insulin resistance in these patients therefore is caused by a combination of a postreceptor defect in insulin action and a decrease in the number of insulin receptors.

Receptor defects

Measurements of insulin binding to circulating monocytes and isolated adipocytes have shown that the ability of these cells to bind insulin was reduced due to a decreased number of cellular insulin receptors, both in patients with type 2 diabetes and in subjects with impaired glucose tolerance. Compared to normal persons binding of insulin to its receptors is already 20% lower in overweight persons, and 50% lower in obese type 2 diabetic patients (48).

Post-receptor defects

Receptor phosphorylation sites

There seem to be 2 different populations of insulin receptors. In healthy individuals 40% of the receptors is capable to autophosphorylate, while 60% is not. In patients with type 2 diabetes only 14% is capable to autophosphorylate. Such disturbances may be caused by changes in the structure of the beta-subunit, for instance based on a change in aminoacid sequence. A different spatial configuration would lead to different acceptor places for phosphorylation. Also, it is possible that serine residues are phosphorylated in preference, which would inhibit the addition of phosphate to tyrosine.

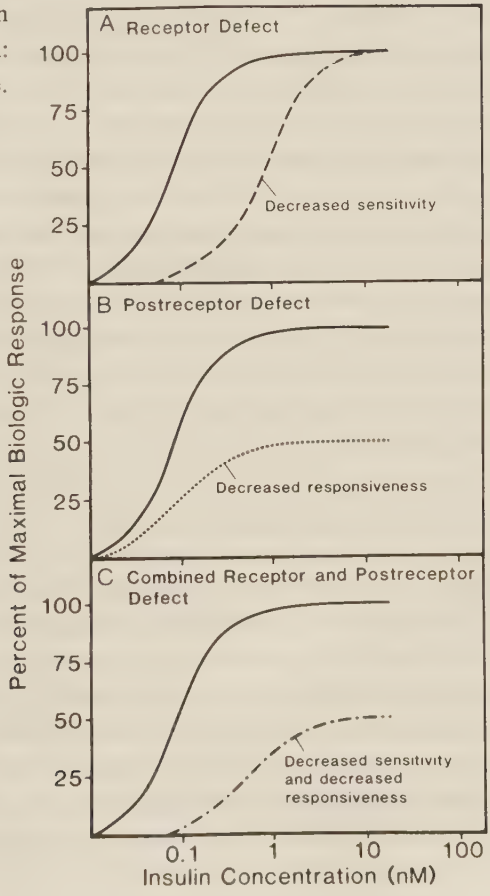

Figure 4. The dose-response curve of insulin action. From: Olefsky JM, Molina JM. In: Diabetes Mellitus, Theory and Practice. p.126.

Glucose transporters

It has recently been demonstrated that the number of glucose transporters is decreased in patients with type 2 diabetes, both in the basal state and in the postprandial -stimulated- state (49,50). Their function is possibly also diminished. Possible causes of the reduction in activity may be changes in structure, dysbalance of other regulatory factors (cAMP, ATP, adenosine), or increased breakdown or turnover (51,52). The latter is supported by the finding that the number of glucose transporters in the intracellular high density subfraction is normal, which may point to a normal (or even increased) rate of synthesis of glucose transporters.

Glucose metabolism

Insulin-mediated, non-oxidative metabolism of glucose is due largely to glycogen synthesis by skeletal muscle. With the application of nuclear magnetic resonance spectroscopy it was demonstrated during a hyperinsulinaemic-glucose-clamp that insulin resistance in type 2 diabetic patients results from a defect in this pathway. Thus, in type 2 diabetic patients impaired glycogen synthesis is the major intracellular metabolic defect responsible for the decrease in nonoxidative and whole-body glucose metabolism (12). Activation by insulin of glycogen synthase phosphatase, an enzyme that dephosphorylates and thus activates glycogen synthase, was shown to be reduced in persons with insulin resistance, and responsible for these findings (13). The mechanism responsible for the reduction of insulin-mediated glucose metabolism is not known. A reduced activity of phospholipase C or diminished synthesis of intermediate messengers like diacylglycerol (DAG) and phospho-inositolglycan (PIG) have been postulated.

Hepatic glucose production

The rate of basal hepatic glucose production is increased compared to normals in both obese and non-obese patients with fasting hyperglycaemia. The dose-response curve for suppression of hepatic glucose production by insulin is shifted to the right both in patients with impaired glucose tolerance and in patients with type 2 diabetes. However, hepatic glucose output can be totally suppressed in all patients with sufficient concentrations of circulating insulin. This demonstrates that on the level of the hepatocytes the defect in insulin sensitivity is due to a decreased number of insulin receptors, whereas it suggests that little or no postreceptor defect is present.

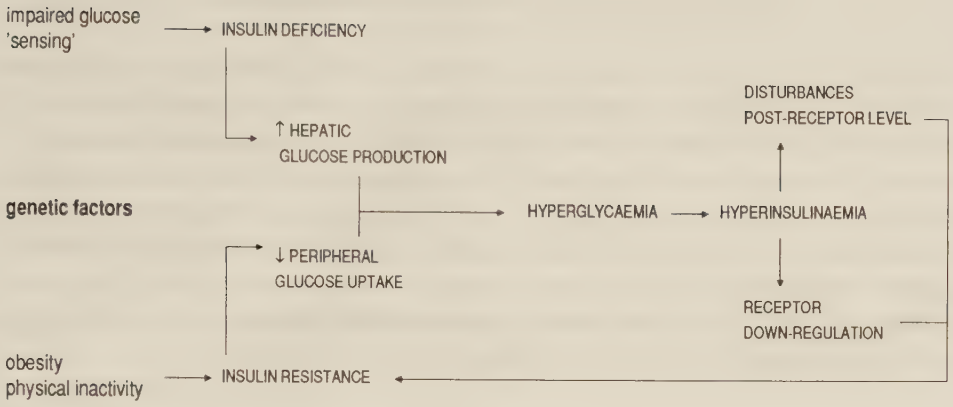

Figure 5. Pathophysiology of type 2 diabetes: the simplified view.

GLUCOSE TOXICITY

A few years ago it was suggested that hyperglycaemia per se could directly impair the secretion of insulin and reduce the insulin-mediated uptake of glucose in peripheral tissues (42,53). This is called the theory of 'glucose toxicity'. It supposes that the basic metabolic derangements in patients with type 2 diabetes are pertubated by the resulting hyperglycaemia (figure 5). Insulin release after intravenous administration of glucose is already impaired in persons with only mild fasting hyperglycaemia (blood glucose > 6.4 mmol/l). With blood glucose levels exceeding 11 mmol/l the B-cells become unresponsive to other secretagogues. The disturbances in insulin release are restored by reducing hyperglycaemia and normalizing glycaemic control, independent of the mode of treatment (diet, sulphonylureas, insulin, or phlorizin, a drug inducing glucuresis) (54,55). There is some experimental evidence suggesting that high glucose levels not only cause functional disturbances, but even may cause irreversible damage to the B-cells. Some, but not all, investigators found that damage could be prevented by reduction of the hyperglycaemia. In addition, in hyperglycaemic states related to obesity insulin resistance is a main feature. Insulin therapy in such cases, and the resulting reduction of blood glucose levels, readily improves insulin action. These beneficial changes may be maintained for a few weeks after insulin withdrawal (56,57).

IS TYPE 2 DIABETES A DISTINCT CLINICAL ENTITY?

Reaven (39) has suggested that type 2 diabetes is not a distinct clinical disorder, but part of a complex of risk factors for cardiovascular disease. This complex comprises disturbances as glucose intolerance, insulin resistance, hyperinsulinaemia, increased very-low-density lipoprotein triglycerides, decreased high-density lipoprotein cholesterol, and hypertension. This approach has considerable implications for the treatment of patients with type 2 diabetes. It necessitates not only the pursuit of good blood glucose control, but places greater emphasis on the treatment of dyslipidaemia, hypertension and obesity to reduce the risk of coronary heart disease (58,59).

CONSEQUENCES OF TYPE 2 DIABETES LATE COMPLICATIONS

Secondary complications (table 2) are frequently observed in patients with type 2 diabetes (60). Estimations of the prevalence of the various complications differ considerably between studies. In the Netherlands, no good epidemiologic surveys concerning the incidence and prevalence of type 2 diabetes in general, and of its complications in particular, are available. The true risk of cardiovascular disease (and other macrovascular and microvascular sequelae) in type 2 diabetic patients is difficult to assess from the literature because of several reasons:

1. Details on the type of diabetes, mode of treatment, severity of associated dyslipidaemia and hypertension are often not given.
2. Bias is introduced due to selection of patients studied (hospital-based surveys, or patients belonging to the practice of a general practitioner).
3. The duration of diabetes, which is sometimes difficult to assess with certainty in type 2 diabetic patients, is often not recorded or not reported.
4. Between different study populations and racial groups, and even within one country large differences in incidence can be found.
5. An increase of cardiovascular disease can already be found in patients with impaired glucose tolerance.
6. Different tools or devices are used to assess the presence or absence of a complication. For instance, the use of sophisticated doppler measurements may increase the number of patients diagnosed to have peripheral arterial disease.

Table 2. Consequences of type 2 diabetes mellitus.

1. Diminished quality of life
2. Increased mortality
3. Acute metabolic complications
   - hyperlipidaemia
   - hyperosmolar non-ketotic coma
4. Chronic complications
   - macroangiopathy: ischaemic heart disease
     cerebrovascular accidents
     peripheral vascular disease
   - hypertension, congestive heart failure
   - peripheral neuropathy: diabetic foot, pain
   - amputations
   - autonomic neuropathy: gastroparesis
     urinary bladder dysfunction
   - microangiopathy: retinopathy, nephropathy
   - cataract

Macrovascular disease

The role of diabetes as a risk factor for cardiovascular disease is well established. Annual incidence of cardiovascular disease among diabetic patients is increased almost 3-fold compared to non-diabetic persons. Atherosclerosis in diabetic patients shows identical development compared to non-diabetic persons, but occurs 10-20 years earlier (61). The risk ratios appear to decrease slightly with advancing age. This may be caused by an increased mortality of diabetic patients due to cardiovascular disease at a younger age. Several factors are involved in the pathogenesis of macrovascular abnormalities in type 2 diabetic patients (table 3). Besides these, the diabetic state is a risk factor itself.

It seems that the development and extent of macroangiopathy is not related to the severity of diabetes (61,62), nor to the form of therapy. Both oral and insulin therapy have failed to lower cardiovascular mortality compared to diet alone (61), although the degree of glycaemic control that was reached might have been insufficient. Some authors have demonstrated a relation between increasing duration of diabetes and the incidence of macrovascular complications; this item however is disputed by others (63). In the Whitehall survey, there was no significant relationship between duration of diabetes and mortality from coro-

Table 3. Possible factors involving earlier atherosclerosis in type 2 diabetes.

Diabetic factors	Classical factors (non-specific)
1. abnormal lipoprotein metabolism	1. hypertension
2. 'non-enzymatic' glycosylation of proteins	2. hypercholesterolaemia
3. glucose toxicity	3. obesity
4. hyperinsulinaemia	4. sedentary lifestyle
5. genetic factors	5. smoking

nary heart disease. Thus, it was stated that type 2 diabetes and coronary heart disease are associated disorders, but that an increased risk of coronary heart disease precedes the development of hyperglycaemia (64,65). However, one confounding factor is the fact that elevated blood glucose levels may already be present for several months or even years before the diagnosis of type 2 diabetes is made. Hence, the true duration of type 2 diabetes can not easily be estimated. As in non-diabetic individuals there exists a clear relationship between the prevalence of macroangiopathy and the age of the patient.

Hypertension

Hypertension is a well-known risk factor for the development of cardiovascular complications. The combination of hypertension and diabetes means a higher risk for retinopathy, nephropathy, myocardial infarction, stroke and peripheral vascular disease. Both diseases occur quite often in one person. Diabetic patients show a prevalence of hypertension 1.2-4.7 times that of non-diabetic persons (66,67). Essential hypertension accounts for the majority of cases of hypertension in diabetes mellitus. Diabetic nephropathy, which occurs in every third individual with type 1 and in every fifth individual with type 2 diabetes after 15 years of diabetes, is another important cause of hypertension. Treatment of hypertension seems to decrease the risk for cardiovascular complications in general, and in patients with diabetic nephropathy it was already shown that normalization of an elevated blood pressure can slow down the decline of kidney function. However, there are no studies yet to establish whether effective antihypertensive treatment may prevent the development or progression of other diabetic angiopathic complications such as retinopathy.

Dyslipidaemia

Lipid abnormalities are often found in type 2 diabetic patients. Elevations of both VLDL ('very-low-density-lipoproteins') and -less frequently- LDL ('low-density-lipoproteins') are reported, as well as decreases in the levels of HDL ('high-density-lipoproteins') (68,69). An increase in VLDL-levels occurs as a consequence of increased synthesis and secretion by the liver, combined with decreased clearance from the circulation. VLDL contain greater amounts of triglycerides. Increased synthesis probably is caused by a higher supply of fatty acids to the liver due to insufficient suppression of peripheral lipolysis based on insulin insensitivity. VLDL clearance is lower due to reduced activity of the enzyme lipoprotein lipase (LPL) (70). Improved diabetic control increases LPL activity, and stimulates VLDL breakdown. The mechanisms responsible for elevated LDL and lower HDL levels are poorly understood (71).

In diabetic patients, elevated triglyceride levels seem to be an independent risk factor for the development of macrovascular disease. In epidemiologic studies it was shown that about 30-35% of diabetic men and 30% of women, aged 50-65 years, showed combined hyperlipidaemia, whereas half of these persons also have low HDL concentrations (72). Combination of diabetes and hypercholesterolaemia conveys a very high risk of developing coronary heart disease and of mortality due to myocardial infarction (73).

Hyperinsulinaemia

Several studies have suggested a relationship between hyperinsulinaemia and ischaemic heart disease (74). Hyperinsulinaemia is associated with a number of cardiovascular risk factors, i.e. high blood pressure, raised triglyceride- and LDL-cholesterol levels, and lower HDL-levels (75). Insulin stimulates arterial smooth muscle cell proliferation, promotes lipid uptake and synthesis in the arterial vascular wall (76), and possibly increases platelet aggregation (77). Although treatment with exogenous insulin may result in high peripheral insulin levels, the hyperglycaemia found in unsatisfactorily controlled diabetics may be more damaging in the longer term.

Non-enzymatic glycosylation

With elevated blood glucose levels glycosylation of proteins will occur. These so-formed Schiff bases then rearrange and will form stable glycosylation products (Amadori rearrangements). Some of these 'early' glycosylation products undergo a complex series of chemical reactions, which will result in the formation of irreversible advanced glycosylation end-products. These products accumulate by forming covalent bonds with amino groups of other proteins, resulting in irreversible changes of function of the various tissue (vessel wall,

collagenous tissue). Cross-linking of extravasated glycosylated plasma lipoproteins has been suggested to play a major role in the development of atherosclerosis in diabetes (78).

Aldose reductase

The polyol pathway has been implicated in the develpoment of diabetic complications, especially in neuropathy and vasculopathy. In the tissues, glucose is converted to sorbitol by the enzyme aldose reductase. Accumulation of sorbitol may result in myo-inositol depletion, which impairs Na,K-ATPase activity through a decrease of intracellular protein kinase C activity (79). This is associated with slowing of nerve conduction, capillary basement membrane thickening, and increased leakage of proteins from the vascular compartiment to the interstitium (80).

Coronary heart disease

In general, a two- to three-fold increase of morbidity and mortality attributed to coronary heart disease (CHD) is demonstrated in diabetic patients over 45 years of age compared with the non-diabetic population (81). The prevalence of CHD is already 3 times elevated in newly-diagnosed non-insulin-dependent diabetes as compared with control subjects (82), and may be as high as 30-40% in this group or among patients with longer term diabetes (83). Diabetic patients have a greater number of vessels involved by coronary artery disease, and an increased extent of fatty streaks, raised atherosclerotic and advanced calcified lesions. CHD is the cause of death in as many as 40-50% of type 2 diabetic patients (61,83).

As recorded in the Framingham Study, the incidence of coronary heart disease was 39.1 per 1000 in men with diabetes between 45 and 74 years, and 27.2 per 1000 for women. In the population of patients without diabetes these figures were 19.1/1000 and 10.2/1000, respectively (81). Asymptomatic myocardial ischaemia, which is an independent predictor of mortality in patients with symptomatically controlled angina pectoris, has been demonstrated in 35% of a group of type 2 diabetic patients (84,85). Prognosis after myocardial infarction is poorer in diabetic patients compared to non-diabetic subjects, with a higher risk of developing cardiogenic shock or arrhythmias. Poor metabolic regulation may aggravate the prognosis for myocardial infarction (86).

Peripheral vascular disease

There exists an increased prevalence of peripheral vascular disease (PVD) among diabetic patients compared to nondiabetic subjects. The incidence and prevalence figures vary because of differences in definition of PVD, the type of diabetes in the patients studied, their age and treatment, and the study methods used. In diabetic PVD the vessels most frequently involved are those below the knee, the tibials and peroneals, and their smaller branches, while the occlusions are often multisegmental. It is evidenced by the presence of intermittent claudication, absence of dorsalis pedis pulses, or arterial calcification (87). At time of diagnosis (when hyperglycemia usually is present for a number of years) 8% of type 2 diabetic patients have evidence of PVD. After 10 years the cumulative incidence averages 30% (88), and after 20 years even 50% (89). Other studies (90) give even higher prevalence figures: absence of ≥ 2 peripheral vascular pulses was noted in 60% of the diabetic patients between 60 and 79 years, against 40% in the nondiabetic individuals. In the Framingham study diabetes was associated with a two- to threefold excess risk of intermittent claudication (81). The presence of PVD predisposes for acute cardiovascular events, such as myocardial infarction and stroke (91).

Sequelae of PVD may be serious infections or ulcers and gangrene, sometimes necessitating amputation (88). The amputation rate in individuals with diabetes is 15 times that of people without diabetes (92). This implies that yearly 1500 amputations are performed in diabetic patients in the Netherlands. Outcome of patients after lower-extremity amputation is rather poor: the 3-year survival rate averages 50% (93). Smoking, hypertension, hyperlipidaemia, hyperglycaemia and neuropathy are known risk factors for amputation (89). Improvement of patient education and foot-care may prevent at least 50% of the amputations within the diabetic population.

Cerebrovascular disease

Stroke occurs two to six times more frequently in diabetic patients compared with nondiabetic subjects (66,94). Type 2 diabetic patients show a 2- to 4-fold increase in risk for death from cerebrovascular disease compared to nondiabetic persons. Stroke accounts for 15% of all deaths in patients with type 2 diabetes (83). The extent and degree of brain damage, as well as short term mortality after an ischaemic stroke is higher in diabetic patients than in nondiabetic persons (94), probably due to the deleterious effects of hyperglycaemia itself (95). Diabetic stroke patients more often have a history of hypertension than diabetic control patients without stroke (96). A greater proportion of diabetic

patients, who have recovered from stroke, will be dependent on others for daily living activities, or admitted to a nursing home for continuous care (97,98).

Microvascular disease

Retinopathy
Retinopathy is observed in 20 to 50% of type 2 diabetic patients, depending on the duration of follow-up after diagnosis of diabetes has been made (99). Almost 80% of patients with diabetes diagnosed at age 30 or older (mainly type 2 diabetic patients) had retinopathy after 15 or more years (100). However, at presentation already 10-20% of patients may have signs of retinopathy. The development of diabetic retinopathy is related to long-term glycaemic control (101-104). The severity of retinopathy was related to a younger age at diagnosis, higher systolic blood pressure, use of insulin and presence of proteinuria (100). Again in the Framingham study, a clear association was observed between the presence of diabetic retinopathy and the occurrence of cardiovascular events (coronary heart disease, stroke, claudication) (105).

Nephropathy
It is estimated that 60% of all patients with end-stage renal disease caused by diabetes have type 2 diabetes. The incidence of diabetic nephropathy is however lower (0-15%) in type 2 compared to type 1 diabetic patients (106). The presence of microalbuminuria is a strong predictor of mortality in type 2 diabetic patients, especially due to cardiovascular disease (107,108). Only 5-10% of them die from renal disease. Progression from micro- to macroalbuminuria may proceed rather rapidly, although considerable intraindividual variation exists (109).

TREATMENT OF PATIENTS WITH TYPE 2 DIABETES

Treatment of patients with type 2 diabetes aims at several goals (110-113):
- relieve of complaints of hyperglycaemia
- improvement in quality of life
- improvement of metabolic derangements (table 4):
  blood glucose control
  lipid disturbances
  hyperinsulinaemia
- reduction of increased body weight

- reduction of increased blood pressure
- reduction of incidence of late complications

It is essential to educate and motivate patients for optimal therapy. Many patients with type 2 diabetes may have frank hyperglycaemia and are prone to develop diabetic complications more rapidly, yet specific symptoms due to the hyperglycaemia seldomly are experienced. A number of therapeutic possibilities exist in the treatment of patients with type 2 diabetes. Dietary advices, aiming at reduction of body weight, and encouragement of regular physical exercise (114,115) form the cornerstone of treatment. In addition, drugs may be prescribed, which decrease the postprandial blood glucose increase, stimulate insulin secretion or improve peripheral insulin action. In a number of cases, administration of insulin may be necessary.

Table 4. Goals of therapy in type 2 diabetes.

	Good	Fair	Poor
Body mass index (kg/m^2)			
male	22 - 25	25 - 27	> 27
female	22 - 24	24 - 26	> 26
Blood glucose (mmol/l)[#]			
fasting	4.4 - 6.7	6.7 - 8.0	> 8.0
postprandial	4.4 - 9.0	9.0 - 11.0	> 11.0
HbA_1 (%)[*]	< 8.0	8.0 - 9.5	> 9.5
Total cholesterol (mmol/l)	< 5.2	5.2 - 6.5	> 6.5
HDL-cholesterol (mmol/l)	> 1.1	0.9 - 1.1	< 0.9
Triglycerides (mmol/l)	< 1.7	1.7 - 2.2	> 2.2
Blood pressure (mmHg)			
systolic	<140	140-160	>160
diastolic	< 85	85-100	>100

[*] HbA_{1c}: value x 0.8;
[#]dependent on age and specific goals.

Dietary advices

The nutritional composition of the diabetic diet is similar to the diet advised for the general population by the Dutch government (116). Diet is the most difficult aspect of treatment (table 5); compliance with the diet is generally low. The amount of calories should be such, that the desirable ('ideal') body weight can be achieved and maintained (117). This means a restriction of energy intake for the obese patients, at an average of 500-1000 kcal below requirements. Although initial dietary prescriptions can result in improved control when serious dietary errors are made (118), weight reduction is necessary to achieve and maintain improved metabolic control on the long term (119-122). Fat intake in the Western population is high; advices concerning fat usually imply a restriction of the intake, ideally to 30% of total energy intake, with less than 10% in the form of saturated fatty acids, about 6 to 8% in the form of polyunsaturated fatty acids, and the remainder as mono-unsaturated fatty acids. Cholesterol intake should not exceed 300 mg per day. Daily protein need averages 12-20% of total dietary energy content.

The amount of carbohydrate should be liberalized to 55-60% of total energy intake, comprising especially complex carbohydrates and foods with high fibre content. Addition of sucrose to the diet (up to 50 grams per day) does not worsen blood glucose control (123,124), nor leads to more marked hypertriglyceridaemia (125). Thus, fastly-resorbed (refined) sugars may be allowed up to 5% of carbohydrate energy intake if incorporated in the normal meals in patients with normal body weight, who do not have carbohydrate induced hyperlipidaemia. For the obese patients the use of sugar is not advisable.

Table 5. Points to consider when prescribing a diabetic diet

1. Treatment: diet, oral hypoglycaemic agents, insulin
2. Body weight
3. Normal daily activities
4. Usual dietary intake and meal pattern
5. Support from family
6. Cooking and shopping abilities; dependence on family or community services
7. Other medical problems or physical disabilities
8. Intelligence; ability to understand the role of diet in the control of diabetes; ability to follow a dietary advice

Partial replacement of complex carbohydrates with mono-unsaturated fatty acids may improve blood glucose control, lower plasma triglycerides and increase HDL-cholesterol (126). The long term effects of diets high in mono-unsaturated fatty acids still needs to be determined.

Diets with a very low amount of calories have been used in several instances (127,128). Although on short term a striking reduction of body weight may be achieved, together with improvement of dyslipidaemia and blood pressure (129), there is little evidence that the weight loss actually is maintained on longer term (130).

Adjuvants to dietary therapy

The use of additional medication may help to control postprandial blood glucose increase, or to achieve weight reduction. The effects of fiber additives, such as guar, have been disappointing, both because of its unpleasant gastrointestinal side-effects, and the little effects on blood glucose control. Their effects on plasma lipids are generally beneficial (131,132). Drugs that exert a competitive inhibition of the enzyme α-glucosidase in the intestine may reduce the postprandial blood glucose rise (133,134). Their place in the long-term therapy of patients with type 2 diabetes has not been established yet. The effects of fish-oil supplementation may be beneficial in case of dyslipidaemia, but detrimental for blood glucose control (135).

Oral hypoglycaemic therapy

Oral hypoglycaemic agents are used in the diabetic patients, who cannot achieve adequate glycaemic control with diet alone. Sulphonylureas (SU) are first line therapy. These drugs promote the release of insulin from the B-cells (136). This effect is possibly evoked by specific receptors on these cells. In addition to this direct effect, sulphonylurea therapy improves B-cell function as a consequence of the reduced blood glucose levels (53,55,137). The improvement of insulin action seen during SU therapy are still a matter of debate: some authors argue that SU exert their major effects on the liver by improving insulin-mediated glycogen formation and lipogenesis and by inhibiting glycogenolysis and gluconeogenesis (138), while others (139) suggested that its effects are secondary to an improvement of postreceptor defects. A decrease of hepatic insulin extraction may be secondary to the increased rate of insulin secretion (136).

There is some evidence that chronic treatment with SU may desensitize the B-cells to this stimulus (139). High concentrations of SU may inhibit insulin biosynthesis *in vitro* (140), and perhaps also *in vivo* (139,141). Resorption of SU may decrease with higher prevailing blood glucose levels (142).

A variety of available SU compounds differ in potency, onset of action and duration of effect (138). Subjective side-effects of sulphonylurea are usually low. Hypoglycaemic reactions are the most serious side-effects, and these may be very prolonged in elderly patients, leading to neurologic damage and even death (136,137,143). The risk of hypoglycaemia is the highest with long-acting compounds, such as chlorpropamide and glibenclamide. Drug interactions (aspirin, sulphonamides), reduced energy intake, and alcohol consumption are precipitating factors (136).

The mechanisms of action of metformin are a matter of debate (136, 144). Increasing glucose transport across the cell membrane in skeletal muscle is one of the main effects (145), together with a suppression of hepatic glucose production (136), and reduced gastrointestinal absorption of glucose. Several authors, however, failed to show any improvement of insulin action with metformin (146,147). Metformin has beneficial effects on elevated LDL-cholesterol and plasma triglyceride levels. The drug rarely causes hypoglycaemia or weight gain. Side effects (gastrointestinal discomfort, diarrhoea) occur in 10-20% of patients. Metformin is contraindicated in patients with renal or hepatic insufficiency, and patients with cardiovascular abnormalities in whom tissue hypoperfusion and anoxia and altered cellular metabolism may cause lactic acid production.

Comparison of sulphonylurea and metformin slightly favoured the glucose-lowering effect of sulphonylurea, although weight loss was greater during metformin (148-150). In the U.K. Prospective Diabetes Study metformin was compared with sulphonylurea in the obese patients only, and resulted in nearly similar reduction of fasting blood glucose (151,152).

Secondary failure to oral agents

Failure to oral hypoglycaemic therapy after an initial favourable response may occur in approximately 5-10% of patients on a yearly basis (153). However, the reported frequency varies considerably, because of the lack of a widely accepted definition of secondary drug failure, and how strict the levels of blood glucose are regarded acceptable or unacceptable. Several factors can attribute to the occurrence of secondary failure, both patient- and disease-related, such as non-compliance with diet or drug therapy, inadequate dose of drug, interruption of drug treatment, intercurrent illness or real failure (islet B-cell "exhaustion") (152-154, table 6).

Table 6. Factors involved in secondary drug failure in type 2 diabetes.

1. non-compliance with diet
2. non-compliance with drug therapy
3. inadequate dose of drug
4. interruption of drug treatment
5. intercurrent illness
6. disturbances resorption of sulphonylurea?
7. reduced B-cell responsiveness to drug
8. real failure (islet B-cell "exhaustion")

Patients failing to sulphonylureas had a lower relative body weight, and lower basal and glucagon-stimulated plasma C-peptide concentrations than patients who were well controlled. There was not a critical C-peptide level discriminating between nonresponders and responders. A subset of patients with specific immunologic characteristics could be determined with a high risk of secondary drug failure and subsequent insulin requirement (154). Recently, it was demonstrated that occurrence of secondary failure was related to the diabetes itself, and probably not due to patient-related factors, such as daily energy intake or physical activity (155).

Insulin therapy

In patients compliant with diet, who show deterioration of blood glucose control on oral hypoglycaemic agents, temporary or permanent insulin therapy is warranted (156). This treatment however poses new problems, such as weight gain, and the risk of hypoglycaemias. Further, the occasional necessity of administering high insulin doses, especially in obese patients, may result in high peripheral insulin levels, which are associated with an increased risk for the development of atherosclerosis and hypertension.

Initial use of insulin in a type 2 diabetic patient is warranted, when there is gross evidence of deficient insulin secretion and action. This can be assessed by biological factors, such as the presence of ketosis or ketonuria, weight loss, or severe hyperglycaemic symptoms, or by biochemical factors, when fasting blood glucose levels exceed 15 mmol/l, or stimulated C-peptide levels are lower than 0.2 nmol/l.

There are few studies which compare the effects of sulphonylurea and insulin on blood glucose control in type 2 diabetic patients who have failed on dietary therapy. Tolazamide and insulin equally improved blood glucose control in obese patients (157). In non-obese type 2 diabetic patients insulin therapy resulted in better blood glucose control than sulphonylureas (158,159). In the U.K. Prospective Diabetes Study an equal effect of sulphonylurea and insulin on blood glucose control in both obese and non-obese patients was found.

Various insulin injection schemes have been proposed, such as once daily regimes of long-acting insulin on waking or retiring, or twice-daily injections. In a small number of patients even multiple subcutaneous injections or CSII have been employed. Twice-daily administration of intermediate-acting or a mixture of fast- and intermediate-acting insulin can be safely instituted on an outpatient base as first regimen (160). In the majority of patients this regimen can optimize blood glucose control. More complicated schemes, such as multiple daily injections or combination of insulin and oral hypoglycaemic agents may be warranted in the younger type 2 diabetic patients, in whom the twice daily regimen fails to restore adequate control (160).

Weight gain during insulin treatment may be troublesome, especially in the obese patient. A small increase in body weight is caused by rehydration, salvage of glucosuric calories, and a positive nitrogen balance. Overinsulinization with the resulting occurrence of overt or inapparent hypoglycaemias, direct stimulation of the appetite by insulin, reduction of energy expenditure and reducton in hyperglycaemic satiety are possible explanations for inadvertent weight gain. Hypoglycaemia during insulin therapy was reported to be as frequent as with chlorpropamide in the U.K. Prospective Study. The incidence of severe hypoglycaemia in insulin-treated patients is reported to be 0.07 per patient and year; this seems to be lower in insulin-treated type 2 diabetic patients (161).

The combined insulin-sulphonylurea therapy in patients with type 2 diabetes mellitus may have several advantages, such as lower insulin requirement, improved and more stable blood glucose control, and less hyperinsulinaemia, and therefore possibly a lower risk for the progression of atherosclerosis (162, 163). The mechanisms by which metabolic control is improved involve an increase in endogenous insulin secretion and possibly extrapancreatic actions of the sulphonylureas on liver and muscle (164). The possible negative effects on lipoprotein metabolism still have to be further explored.

Treatment of dyslipidaemia

In the treatment of diabetic dyslipidaemia dietary advices, weight reduction, regular physical exercise and cessation of smoking take a central place, but their effect is only limited. For drug therapy HMG CoA reductase inhibitors may be the drugs of choice in type 2 diabetic patients with elevated LDL-cholesterol and moderate hypertriglyceridaemia (165,166). Alternatively, gemfibrozil (167) or other fibrate derivatives (168) may be more beneficial in patients with severe hypertriglyceridaemia and moderately elevated LDL-cholesterol. These drugs also increase HDL levels to a greater extent than the inhibitors of cholesterol synthesis. Although the combination of HMG CoA reductase inhibitors with gemfibrozil looks very promising considering the mode of action of these drugs, caution should be taken because of recent reports concerning the occurrence of side-effects, such as severe rhabdomyolysis (169).

Treatment of elevated blood pressure

In diabetes, there is a relationship between hyperinsulinaemia, insulin resistance and hypertension as well (170). This stresses the importance of antihypertensive drugs that, ideally, should not alter glucose and lipid metabolism (171). However, drug treatment of hypertension in patients with diabetes mellitus may cause problems. Often used drugs as diuretics and beta-adrenoreceptor blocking agents have a clearly negative effect on glucose and lipoprotein metabolism (172). Thiazide diuretics may lead to deterioration of diabetic control, possibly mediated through hypokaliaemia with impaired release of insulin and an increase in insulin resistance. Most diuretics also cause an increase of plasma cholesterol and triglycerides. Although studies in non-diabetic hypertensive patients have shown that these alterations in lipoproteins may be transient, this is not shown for diabetes. Betablockers can worsen glucose tolerance by a direct inhibition of insulin secretion and/or increased alpha-receptor-mediated hepatic glycogenolysis. Further, they can mask some of the signs and symptoms of low blood glucose levels and also impair the recovery from hypoglycaemia. Betablockers have also turned out to increase serum triglyceride levels and reduce HDL-cholesterol levels. Another adverse effect of betablockers is impotence, especially, but not only, in patients with autonomic neuropathy. The alpha adrenergic inhibitor prazosin, the vasodilator hydralazine and central sympatholytic agents as methyldopa and clonidine can lead to orthostatic hypotension. These drugs have no unfavourable effect on glucose tolerance or the lipid profile. The effects of newer antihypertensive drugs as ACE-inhibitors (173,174) and calcium entry blockers on glucose

tolerance and the lipid profile have not been fully established yet. Literature data so far have indicated no important negative effects of both drugs on glucose tolerance, neither in non-diabetic persons with hypertension, nor in patients with diabetes mellitus (175,176). Hence, these drugs appear to be a good choice for use in diabetic patients with cardiovascular diseases.

THE COSTS OF TYPE 2 DIABETES MELLITUS

Estimations on the social impact of type 2 diabetes mellitus have to take into account the economic burden of the disease as well as its related morbidity and mortality. Thus, the total economic costs in 1986 in the U.S.A. regarding diabetes care, costs attributable to an excess prevalence of vascular complications, and productivity lost due to disability, morbidity and premature mortality were estimated to amount 20 billion U.S. dollar (177). In this study, prevalence of type 2 diabetes was estimated to be 55 per 1000 persons between 45 and 65 years, and 100 per 1000 persons older than 65 years. Thus, a total number of 5.8 million persons were suffering from diabetes. The yearly costs of diabetes care to the National Health Service of 279 million U.K. pounds may be an underestimation (178). There are clear signs of a rapidly rising prevalence of persons with type 2 diabetes, both due to a real increase and to earlier detection of the disease. In addition, to every known diabetic subject there is another person whose diabetes is still undiscovered (179). It is estimated that within 15 years the number of persons in the Netherlands suffering from type 2 diabetes will have increased with 40%. This will place a large burden on financial and personal resources of the (Dutch) Health Care system (180).

REFERENCES

1. Espinal J. Understanding insulin action: principles and molecular mechanisms. 1989, Ellis Horwood Limited, Chichester, UK.
2. WHO Expert Committee on Diabetes Mellitus. Technical Report Series 646. Geneva: World Health Organization, 1985.
3. DeFronzo RA. The triumvirate: beta-cell, muscle, liver: a collusion responsible for NIDDM. Diabetes 1988; 37: 667-687.
4. Efendic S, Luft R, Wajngot A. Aspects of the pathogenesis of type 2 diabetes. Endocrine Rev 1984; 5: 395-410.
5. DeFronzo RA, Ferrannini E, Koivisto V. New concepts in the pathogenesis and treatment of noninsulin-dependent diabetes mellitus. Am J Med 1983; 74 (suppl): 52-81.

6. Bogardus C, Lillioja S, Howard BV, Reaven GM, Mott D. Relationships between insulin secretion, insulin action, and fasting plasma glucose concentrations in nondiabetic and non-insulin-dependent diabetic subjects. J Clin Invest 1984; 74: 1238-1246.
7. Robertson RP. Type II diabetes, glucose "non-sense", and islet desensitization. Diabetes 1989; 38: 1501-1505.
8. Ward WK, Beard JC, Halter JB, Pfeifer MA. Porte D Jr. Pathophysiology of insulin secretion in non-insulin dependent diabetes mellitus. Diabetes Care 1984; 7: 491-502.
9. DeFronzo RA, Simonson D, Ferrannini E. Hepatic and peripheral insulin resistance: a common feature of type II (noninsulin-dependent) and type I (insulin-dependent) diabetes mellitus. Diabetologia 1982; 23: 313-319.
10. Olefsky JM. The insulin receptor: its role in insulin resistance in obesity and diabetes. Diabetes 1976; 25: 1154-1165.
11. Rizza RA, Mandarino LJ, Gerich JE. Mechanism and significance of insulin resistance in non-insulin-dependent diabetes mellitus. Diabetes 1981; 30: 990-995.
12. Shulman GI, Rothman DL, Jue T, Stein P, DeFronzo RA, Shulman RG. Quantitation of muscle glycogen synthesis in normal subjects and subjects with non-insulin-dependent diabetes by ^{13}C nuclear magnetic resonance spectroscopy. New Engl J Med 1990; 322: 223-228.
13. Bogardus C, Lillioja S. Where all the glucose doesn't go in non-insulin-dependent diabetes mellitus. New Engl J Med 1990; 322: 262-263.
14. Meglasson MD, Matschinsky FM. Pancreatic islet glucose metabolism and regulation of insulin secretion. Diabetes/Metab Rev 1986; 2: 215-241.
15. Lenzen S, Panten U. Signal recognition by pancreatic B-cells. Biochem Pharmac 1988; 37: 371-378.
16. Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Mott DM, Bennett PH. Sequential changes in serum insulin concentration during development of non-insulin-dependent diabetes. Lancet 1989; 1: 1356-1359.
17. Temple RC, Carrington CA, Luzio SD, et al. Insulin deficiency in non-insulin-dependent diabetes. Lancet 1989; i: 293-295.
18. Hosker JP, Rudenski AS, Burnett MA, Matthews DR, Turner RC. Similar reduction of first- and second-phase B-cell responses at three different glucose levels in type II diabetes and the effect of gliclazide therapy. Metabolism 1989; 38: 767-772.
19. Pfeifer MA, Halter JB, Porte D Jr. Insulin secretion in diabetes mellitus. Am J Med 1981; 70: 579-588.
20. Ward WK, Bolgiano DC, McKnight B, Halter JB, Porte Jr D. Diminished B cell secretory capacity in patients with non-insulin-dependent diabetes mellitus. J Clin Invest 1984; 74: 1318-1328.
21. Van Haeften TW. Insulin secretion; stimulation by arginine and hyperglycemic glucose clamp (Thesis). 1990, Amsterdam.
22. Polonsky KS, Given BD, Hirsch LJ, *et al.* Abnormal patterns of insulin secretion in non-insulin-dependent diabetes mellitus. N Engl J Med 1988; 318: 1231-1239.
23. O'Rahilly S, Turner RC, Matthews DR. Impaired pulsatile secretion of insulin in relatives of patients with non-insulin-dependent diabetes. N Engl J Med 1988; 318: 1225-1230.
24. Brunzell JD, Robertson RP, Lerner RL, Hazzard WR, Ensinck JW, Bierman EL, Porte D Jr. Relationships between fasting plasma glucose levels and insulin secretion during intravenous glucose tolerance tests. J Clin Endocrinol Metab 1976; 42: 222-229.

25. Gjessing HJ, Reinholdt B, Pedersen O. The plasma C-peptide and insulin responses to stimulation with intravenous glucagon and a mixed meal in well-controlled type 2 (non-insulin-dependent) diabetes mellitus: dependency on acutely established hyperglycaemia. Diabetologia 1989; 32: 858-863.
26. Scheen AJ, Paolisso G, Juchmes J, Lefebvre PJ. Insulin secretion rate after intravenous glucagon injection: kinetics reproducibility and potentiation by increasing initial blood glucose levels. Diabetologia 1989; 32: 538A.
27. Lefèbvre PJ, Paolisso G, Scheen AJ, Henquin JC. Pulsatility of insulin and glucagon release: physiological significance and pharmacological implications. Diabetologia 1987; 30: 443-452.
28. Lang DA, Matthews DR, Turner RC. Brief, irregular oscillations of basal plasma insulin and glucose concentrations in diabetic man. Diabetes 1981; 30: 435-439.
29. Rahier J. The diabetic pancreas: a pathologist's view. In: The pathology of the endocrine pancreas in diabetes. Lefèbvre PJ, Pipeleers DG (eds). Springer-Verlag, Berlin, 1988.
30. Opie E. The relation of diabetes mellitus to lesions of the pancreas. Hyaline degeneration of the islets of Langerhans. J Exp Med 1901; 5: 527-540.
31. Westermark P, Wernstedt C, Wilander E, Hayden DW, O'Brien TD, Johnson KH. Amyloid fibrils in human insulinoma and islets of Langerhans of the diabetic rat are derived from a neuropeptide-like protein also present in normal islet cells. Proc Natl Acad Sci 1987; 84: 3881-3885.
32. Clark A. Islet amyloid and type 2 diabetes. Diabetic Med 1989; 6: 561-567.
33. Maloy AL, Longnecker DS, Greenberg ER. The relation of islet amyloid to the clinical type of diabetes. Human Pathol 1981; 12: 917-922.
34. Clark A, Saad MF, Nezzer T, et al. Islet amyloid polypeptide in diabetic and non-diabetic Pima Indians. Diabetologia 1990; 33: 285-289.
35. Brain SD, Williams TJ. Substance P regulates the vasodilator activity of calcitonin gene-related peptide. Nature 1988; 335: 73-75.
36. Molina JM, Cooper GJS, Leighton B, Olefsky JM. Induction of insulin resistance *in vivo* by amylin and calcitonin gene-related peptide. Diabetes 1990; 39: 260-265.
37. Johnson KH, O'Brien TD, Betsholtz C, Westermark P. Islet amyloid, islet-amyloid polypeptide, and diabetes mellitus. N Engl J Med 1989; 321: 513-518.
38. Reaven GM. Insulin secretion and insulin action in non-insulin-dependent diabetes mellitus: which defect is primary? Diabetes Care 1984; 7 (suppl. 1): 17-24.
39. Reaven GM. Role of insulin resistance in human disease. Diabetes 1988; 37: 1595-1607.
40. Chen Y, Swislocki A, Reaven G. Resistance to insulin suppression of plasma free fatty acid concentrations and insulin stimulation of glucose uptake in non-insulin-dependent diabetes mellitus. J Clin Endocrinol Metabol 1987; 64: 17-21.
41. Fraze E, Donner CC, Swislocki ALM, Chiou Y-AM, Chen Y-DI, Reaven GM. Ambient plasma free fatty acid concentrations in non-insulin-dependent diabetes mellitus: evidence for insulin resistance. J Clin Endocrinol Metabol 1985; 61: 807-811.
42. Unger RH, Grundy S. Hyperglycaemia as an inducer as well as a consequence of impaired islet cell function and insulin resistance: implications for the management of diabetes. Diabetologia 1985; 28: 119-121.
43. Becker AB, Roth RA. Insulin receptor structure and function in normal and pathological conditions. Annu Rev Med 1990; 41: 99-115.
44. Rosen OM. Structure and function of insulin receptors. Diabetes 1989; 38: 1508-1511.

45. Carpentier J-L. The cell biology of the insulin receptor. Diabetologia 1989; 32: 627-635.
46. Saltiel AR. Second messengers of insulin action. Diabetes Care 1990; 13: 244-256.
47. Olefsky JM, Molina JM. Insulin resistance in man. In: Ellenberg and Rifkin's Diabetes Mellitus: Theory and Practice. Rifkin H, Porte D Jr, Eds. 4th Edition, Elsevier Science Publishing Co, New Hyde Park, NY, 1990.
48. Olefsky JM, Garvey WT, Henry RR, Brillon D, Matthaei S, Freidenberg GR. Cellular mechanisms of insulin resistance in non-insulin-dependent (type II) diabetes. Am J Med 1988; 85 (suppl. 5A): 86-105.
49. Klip A, Paquet MR. Glucose transport and glucose transporters in muscle and their metabolic regulation. Diabetes Care 1990; 13: 228-243.
50. Kahn BB, Flier JS. Regulation of glucose-transporter gene expression *in vitro* and *in vivo*. Diabetes Care 1990; 13: 548-564.
51. Kasanicki MA, Pilch PF. Regulation of glucose-transporter function. Diabetes Care 1990; 13: 219-227.
52. Joost HG, Weber TM. The regulation of glucose transport in insulin-sensitive cells. Diabetologia 1988; 32: 831-838.
53. Rossetti L, Giaccari A, DeFronzo RA. Glucose toxicity. Diabetes Care 1990; 13: 610-630.
54. Hughes TA, Gwynne JT, Switzer BR, Herbst C, White G. Effects of caloric restriction and weight loss on glycemic control, insulin release and resistance, and atherosclerotic risk in obese patients with type II diabetes mellitus. Am J Med 1984; 77: 7-17.
55. Kosaka K, Kuzuya T, Akanuma Y, Hagura R. Increase in insulin response after treatment of overt maturity-onset diabetes is independent of the mode of treatment. Diabetologia 1980; 18: 23-28.
56. Kolterman OG, Olefsky JM. The impact of sulfonylurea treatment upon the mechanisms responsible for the insulin resistance in type II diabetes. Diabetes Care 1984; 7 (suppl.1): 81-88.
57. Scarlett J, Gray R, Griffin J, Olefsky J, Kolterman OG. Insulin treatment reverses the insulin resistance of type II diabetes mellitus. Diabetes Care 1982; 5: 353-363.
58. Zimmet P. Non-insulin-dependent (type 2) diabetes mellitus: does it really exist? Diabetic Med 1989; 6: 728-735.
59. Editorial. Type 2 diabetes or NIDDM: looking for a better name. Lancet 1989; i: 589-590.
60. Nathan DM, Singer DE, Godine JE, Perlmuter LC. Non-insulin-dependent diabetes in older patients - complications and risk factors. Am J Med 1986; 81: 837-842.
61. Fein FS, Scheuer J. Heart disease in diabetes. In: Ellenberg and Rifkin's Diabetes mellitus: Theory and Practice. Rifkin H, Porte D Jr, Eds. 4th Edition, Elsevier Science Publishing Co, New Hyde Park, NY, 1990.
62. Keen H, Jarrett RJ, Fuller JH, McCartney P. Hyperglycaemia and arterial disease. Diabetes 1981; 30 (suppl.): 49-53.
63. Jarrett RJ. Epidemiology and public health aspects of non-insulin-dependent diabetes mellitus. Epidemiol Rev 1989; 11: 151-171.
64. Jarrett RJ. Type II (non-insulin-dependent) diabetes mellitus and coronary heart disease - chicken, egg or neither? Diabetologia 1984; 126: 99-102.
65. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Cardiovascular risk factors in confirmed prediabetic individuals - does the clock for coronary heart disease start ticking before the onset of clinical diabetes? JAMA 1990; 263: 2893-2898.

66. Roccella EJ, on behalf of the Working Group on Hypertension in Diabetes. Statement on hypertension in diabetes mellitus. Arch Intern Med 1987; 147: 830-842.
67. Drury PL. Non-insulin-dependent diabetes and hypertension. In: Baillière's Clinical Endocrinology and Metabolism, Non-insulin-dependent diabetes. Nattrass M, Hale PJ, Eds. London, 1988.
68. Reaven GM. Abnormal lipoprotein metabolism in non-insulin-dependent diabetes mellitus. Am J Med 1987; 83 (suppl.3A): 31-40.
69. Betteridge DJ. Lipids, diabetes and vascular disease: the time to act. Diabetic Med 1989; 6: 195-218.
70. Billingham MS, Milles JJ, Bailey CJ, Hall RA. Lipoprotein subfraction composition in non-insulin-dependent diabetes treated by diet, sulphonylurea, and insulin. Metabolism 1989; 38: 850-857.
71. Elkeles RS, Rains SGH, Wilson GA, Richmond W. Does glycaemic control affect high density lipoprotein cholesterol (HDL-C) in type II diabetes. A prospective study. Diabetologia 1987; 30 (suppl.): 516a.
72. Assmann G, Schulte H. Diabetes mellitus and hypertension in the elderly: concomitant hyperlipidemia and coronary heart disease risk. Am J Cardiol 1989; 63: 33H-37H.
73. Rosengren A, Welin L, Tsipogianni A, Wilhelmsen L. Impact of cardiovascular risk factors on coronary heart disease and mortality among middle aged diabetic men: a general population study. Br Med J 1989; 299: 1127-1131.
74. Stout RW. Insulin and atheroma - 20-yr perspective. Diabetes Care 1990; 13: 631-654.
75. Jarrett RJ. Is insulin atherogenic? Diabetologia 1988; 31: 71-75.
76. Stolar MW. Atherosclerosis in diabetes: the role of hyperinsulinemia. Metabolism 1988; 37 (suppl. 1): 1-9.
77. Robertson DA, Hale PJ, Nattrass M. Macrovascular disease and hyperinsulinaemia. In: Baillière's Clinical Endocrinology and Metabolism, Non-insulin-dependent diabetes. Nattrass M, Hale PJ, Eds. London, 1988.
78. Brownlee M, Cerami A, Vlassara H. Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications. N Engl J Med 1988; 318: 1315-1321.
79. Cogan DG. Aldose reductase and complications of diabetes. Ann Intern Med 1984; 101: 82-91.
80. Tilton RG, Chang K, Pugliese G, et al. Prevention of hemodynamic and vascular albumin filtration changes in diabetic rats by aldose reductase inhibitors. Diabetes 1989; 37: 1258-1270.
81. Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the Framingham study. Circulation 1979; 59: 8-13.
82. Uusitupa M, Siitonen O, Aro A, Pyorala K. Prevalence of coronary heart disease, left ventricular failure and hypertension in middle-aged, newly diagnosed type 2 (non-insulin-dependent) diabetic subjects. Diabetologia 1985; 28: 22-27.
83. Panzram G. Mortality and survival in type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 1987; 30: 123-131.
84. Koistinen MJ. Prevalence of asymptomatic myocardial ischaemia in diabetic subjects. Brit Med J 1990; 301: 92-95.
85. Chiariello M, Indolfi C, Cotecchia MR et al. Asymptomatic transient ST changes during ambulatory ECG monitoring in diabetic patients. Am Heart J 1985; 110: 529-535.

86. Rytter L, Troelsen S, Beck-Nielsen H. Prevalence and mortality of acute myocardial infarction in patients with diabetes. Diabetes Care 1985; 8: 230-234.
87. Laakso M, Ronnemaa T, Pyorala K, Kallio V, Puukka P, Penttila I. Atherosclerotic vascular disease and its risk factors in non-insulin-dependent diabetic and non-diabetes subjects in Finland. Diabetes Care 1988; 11: 449-463.
88. Kreines K, Johnson E, Albrink M, et al. The course of peripheral vascular disease in non-insulin-dependent diabetes. Diabetes Care 1985; 8: 235-243.
89. Levin ME, Sicard GA. Peripheral vascular disease in the person with diabetes. In: Ellenberg and Rifkin's Diabetes mellitus: Theory and Practice. Rifkin H, Porte D Jr, Eds. 4th Edition, Elsevier Science Publishing Co, New Hyde Park, NY, 1990.
90. Pyörälä K, Laakso M. Macrovascular disease in diabetes mellitus. In: Mann JI, Pyörälä K, Teuscher K, eds. Diabetes in epidemiological perspective. Edinburgh-London, Churchill-Livingstone 1983: 183-231.
91. Abbott RD, Brand FN, Kannel WB. Epidemiology of some peripheral arterial findings in diabetic men and women: experiences from the Framingham study. Am J Med 1990; 88: 376-381.
92. Bild DE, Selby JV, Sinnock P, Browner WS, Braveman P, Showstack JA. Lower-extremity amputation in people with diabetes - epidemiology and prevention. Diabetes Care 1989; 12: 24-31.
93. Osmundson PJ, O'Fallon WM, Zimmerman BR, Kazmier FJ, Langworthy AL, Palumbo PJ. Course of peripheral occlusive arterial disease in diabetes: vascular laboratory assessment. Diabetes Care 1990; 13: 143-152.
94. Asplund K, Hägg E, Helmers C, Lithner F, Strand T, Wester P-O. The natural history of stroke in diabetic patients. Acta Med Scand 1980; 207: 417-424.
95. Pulsinelli WA, Levy DE, Sigsbee B, Scherer P, Plum F. Increased damage after ischemic stroke in patients with hyperglycemia with or without established diabetes mellitus. Am J Med 1983; 74: 540-544.
96. Lithner F, Asplund K, Eriksson S, Hagg E, Strand T, Wester P-O. Clinical characteristics in diabetic stroke patients. Diabete & Metabolisme 1988; 14: 15-19.
97. Mooradian AD, Osterweil D, Petrasek D, Morley JE. Diabetes mellitus in elderly nursing home patients. A survey of clinical characteristics and management. J Am Geriatr Soc 1988; 36: 391-396.
98. Wolffenbuttel BHR, Van Vliet S, Knols AJF, Slits WLH, Sels JPJE, Nieuwenhuijzen Kruseman AC. Clinical characteristics and management of diabetic patients residing in a nursing home. submitted;
99. Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4400 patients observed between 1947 and 1973. Diabetes Care 1978; 1: 168-188 and 252-263.
100. Klein R, Klein BEK, Moss SE, Davis MD, De Mets DL. The Wisconsin Epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy, when age at diagnosis 30 or more years. Arch Ophthalmol 1984; 102: 527-532.
101. Nathan DM, Singer DE, Godine JE, Hodgson C, Harrington CH, Perlmutter LC. Retinopathy in older type II diabetics. Association with glucose control. Diabetes 1986; 35: 797-801.
102. Klein R, Klein BEK, Moss SE, Davis MD, De Mets DL. Glycosylated hemoglobin predicts the incidence and progression of diabetic retinopathy. JAMA 1988; 260: 2864-2871.

103. McCance DR, Atkinson AB, Hadden DR, Archer DB, Kennedy L. Long-term glycaemic control and diabetic retinopathy. Lancet 1989; ii: 824-828.
104. Howard-Williams J, Hillson RM, Bron A, Awdry P, Mann JI, Hockaday DK. Retinopathy is associated with higher glycaemia in maturity-onset diabetes. Diabetologia 1984; 27: 198-202.
105. Hiller R, Sperduto RD, Podgor MJ, Ferris FL, Wilson PWF. Diabetic retinopathy and cardiovascular disease in type II diabetics. The Framingham heart study and the Framingham eye study. Am J Epidemiol 1988; 128: 402-409.
106. Selby JV, FitzSimmons SC, Newman JM, Katz P, Sepe S, Showstack J. The natural history and epidemiology of diabetic nephropathy - implications for prevention and control. JAMA 1990; 263: 1954-1960.
107. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. New Engl J Med 1984; 310: 356-360.
108. Schmitz A, Vaeth M. Microalbuminuria: a major risk factor in non-insulin-dependent diabetes. A 10-year follow-up study of 503 patients. Diabetic Med 1988; 5: 126-134.
109. Cooper ME, Frauman A, O'Brien RCO, Seeman E, Murray RML, Jerums G. Progression of proteinuria in type 1 and type II diabetes. Diabetic Med 1988; 5: 361-368.
110. Alberti KGMM, Gries FA. Management of non-insulin-dependent diabetes mellitus in Europe: a consensus view. Diabetic Med 1988; 5: 275-281.
111. Skyler JS. Non-insulin-dependent diabetes mellitus: a clinical strategy. Diabetes Care, 1984; 7 (suppl.1): 118-129.
112. Lipson LG, Lipson M. The therapeutic approach to the obese maturity-onset diabetic patient. Arch Intern Med 1984; 144: 135-138.
113. Jaspan JB. Monitoring and controlling the patient with non-insulin-dependent diabetes mellitus. Metabolism 1987; 36 (suppl. 1): 22-27.
114. Schneider SH, Ruderman NB. Exercise and NIDDM. Technical Review. Diabetes Care 1990; 13: 785-789.
115. Bogardus C, Ravussin E, Robbins DC, Wolfe RR, Horton ES, Sims EAH. Effects of physical training and diet therapy on carbohydrate metabolism in patients with glucose tolerance and non-insulin-dependent diabetes mellitus. Diabetes 1984; 33: 311-318.
116. Heine RJ, Schouten JA. Het diabetes-dieet: niet anders dan voeding voor gezonde mensen. Ned Tijdschr Geneeskd 1984; 128: 1524-1528.
117. Wales JK. Treatment of type 2 (non-insulin-dependent) diabetic patients with diet alone. Diabetologia 1982; 23: 240-245.
118. Wolffenbuttel BHR, Weber RFA, Verschoor L. Improved insulin secretion in NIDDM by strict dietary control not accompanied by weight reduction. Diab Res Clin Pract 1985; 1: S607.
119. Hadden DR, Montgomery DAD, Skelly RJ, et al. Maturity onset diabetes mellitus: response to intensive dietary management. Br Med J 1975; 2: 276-278.
120. Hadden DR, Blair ALT, Wilson EA, et al. Natural history of diabetes presenting age 40-69 years: a prospective study of the influence of intensive dietary therapy. Quart J Med 1986; 59: 579-598.
121. Henry RR, Wallace P, Olefsky JM. Effects of weight loss on mechanisms of hyperglycemia in obese non-insulin-dependent diabetes mellitus. Diabetes 1986; 35: 990-998.

122. Wolffenbuttel BHR, Weber RFA, Koetsveld PM van, Verschoor L. Limitations of dietary therapy in the treatment of patients with type II diabetes mellitus. Int J Obesity 1989; 13: 173-182.
123. Bantle JP, Laine DC, Thomas JW. Metabolic effects of dietary fructose and sucrose in types I and II diabetic subjects. JAMA 1986; 256: 3241-3246.
124. Peterson DB, Lambert J, Gerring S, et al. Sucrose in the diet of diabetic patients - just another carbohydrate? Diabetologia 1986; 29: 216-220.
125. Jellish WS, Emanuele MA, Abraira C. Graded sucrose/carbohydrate diets in overtly hypertriglyceridemic diabetic patients. Am J Med 1984; 77: 1015-1022.
126. Garg A, Bonanome A, Grundy SM, Zhang Z-J, Unger RH. Comparison of a high-carbohydrate diet with a high-monounsaturated-fat diet in patients with non-insulin-dependent diabetes mellitus. New Engl J Med 1988; 319: 829-834.
127. Henry FR, Wiest-Kent TA, Schaeffer OG, Olefsky JM. Metabolic consequences of a very-low-caloric diet therapy in obese non-insulin-dependent diabetic and non-diabetic subjects. Diabetes 1986; 35: 155-164.
128. Krotkiewski M, Toss L, Bjorntorp P, Holm G. The effects of a very-low calorie diet with and without chronic exercise on thyroid and sex hormones, plasma proteins, oxygen uptake, insulin and C-peptide concentrations in obese women. Int J Obesity 1981; 5:287-293.
129. Uusitupa MIJ, Laakso M, Sarlund H, Majander H, Takala J, Penttilä I. Effects of a very-low-calorie diet on metabolic control and cardiovascular risk factors in the treatment of obese non-insulin-dependent diabetics. Am J Clin Nutr 1990; 51: 768-773.
130. Van Dale D. Diet and exercise in the treatment of obesity (thesis). University of Limburg, 1989.
131. Sels JPJE, Postmes ThJ, Wolffenbuttel BHR, Nieuwenhuijzen Kruseman AC. Dietary fibre in the management of diabetes mellitus. Neth J Med 1991; 38: (in press).
132. O'Dea K, Traianedes K, Ireland P, et al. The effects of diet differing in fat, carbohydrate, and fiber on carbohydrate and lipid metabolism in type II diabetes. J Am Diet Assoc 1989; 89: 1076-1086.
133. Hillebrand I. Pharmacological modification of digestion and absorption. Diabetic Medicine 1987; 4: 147-150.
134. Kingma PJ, Menheere PPCA, Sels JPJE, Nieuwenhuijzen Kruseman AC. Efficacy of the alpha-glucosidase inhibitor miglitol (BAY m 1099) in relation to the starch content in food in NIDDM subjects. Diabetes Care 1991(in press).
135. Borkman M, Chisholm DJ, Furler SM, et al. Effects of fish oil supplementation on glucose and lipid metabolism in NIDDM. Diabetes 1989; 38: 1314-1319.
136. Gerich JE. Drug therapy - oral hypoglycemic agents. New Engl J Med 1989; 321: 1231-1245.
137. Lebovitz HE. Oral hypoglycemic agents. In: The Diabetes Annual/3. Alberti KGMM and Krall LP (eds), Elsevier, Amsterdam, The Netherlands, 1987.
138. Beck-Nielsen H, Hother-Nielsen O, Pedersen O. Mechanism of action of sulphonylureas with special reference to the extrapancreatic effect: an overview. Diabetic Med 1988; 5: 613-620.
139. Melander A. Sulphonylureas in the treatment of non-insulin-dependent diabetes. In: Baillière's Clinical Endocrinology and Metabolism, Non-insulin-dependent diabetes. Nattrass M, Hale PJ, Eds. London, 1988.

140. Andersson A, Borg LAH. Effects of glipizide on the insulin production by isolated mouse pancreatic islets. Acta Endocrinol 1980; 239 (suppl): 37-41.
141. Stenman S, Groop P-H, Laakkonen K, Wahlin-Boll E, Melander A. Relationship between sulfonylurea dose and metabolic effect. Diabetes 1990; 39 (suppl 1): 108A.
142. Groop LC, Luzi L, DeFronzo RA, Melander A. Hyperglycaemia and absorption of sulphonylurea drugs. Lancet 1989; ii: 129-130.
143. Asplund K, Wiholm B-E, Lithner F. Glibenclamide-associated hypoglycaemia: a report on 57 cases. Diabetologia 1983; 24: 412-417.
144. Vigneri R, Goldfine ID. Role of metformin in treatment of diabetes mellitus. Diabetes Care 1987; 10: 118-122.
145. Klip A, Leiter LA. Cellular mechanism of action of metformin. Diabetes Care 1990; 13: 696-704.
146. Pedersen O, Hother-Nielsen O, Bak J, Richelsen B, Beck-Nielsen H, Schwartz Sorensen N. The effects of metformin on adipocyte insulin action and metabolic control in obese subjects with type 2 diabetes. Diabetic Med 1988; 6: 249-256.
147. Wu M-S, Johnston P, Sheu WH-H, et al. Effect of metformin on carbohydrate and lipoprotein metabolism in NIDDM patients. Diabetes Care 1990; 13: 1-8.
148. Rains SGH, Wilson GA, Richmond W, Elkeles RS. The effect of glibenclamide and metformin on serum lipoproteins in type 2 diabetes. Diabetic Med 1988; 5: 653-658.
149. Josephkutty S, Potter JM. Comparison of tolbutamide and metformin in elderly diabetic patients. Diabetic Med 1990; 7: 510-514.
150. McAlpine LG, McAlpine CH, Waclawski ER, Storer AM, Kay JW, Frier BM. A comparison of treatment with metformin and gliclazide in patients with non-insulin-dependent diabetes. Eur J Clin Pharmacol 1988; 34: 129-132.
151. UK Prospective study of therapies of maturity-onset diabetes: I. Effect of diet, sulphonylurea, insulin or biguanide therapy on fasting plasma glucose and body weight over one year. Diabetologia 1983; 24: 404-411.
152. UK Prospective study of therapies of maturity-onset diabetes: II. Reduction in Hba1c with basal insulin supplement, sulfonylurea, or biguanide therapy. Diabetes 1985; 34: 793-798.
153. Thoelke H, Ratzmann KP. Häufigkeit des Sekundärversagens einer Sulfonylharnstofftherapie - Epidemiologische Untersuchung. Dtsch Med Wschr 1989; 114: 580-583.
154. Groop LC, Pelkonen R, Koskimies S, Bottazzo GF, Doniach D. Secondary failure to treatment with oral antidiabetic agents in non-insulin-dependent diabetes. Diabetes Care 1986; 9: 129-133.
155. Groop L, Schalin C, Franssila-Kallunki A, Widén E, Ekstrand A, Eriksson J. Characteristics of non-insulin-dependent diabetic patients with secondary failure to oral antidiabetic therapy. Am J Med 1989; 87: 183-190.
156. Heine RJ. Insulin treatment of non-insulin-dependent diabetes mellitus. In: Baillière's Clinical Endocrinology and Metabolism, Non-insulin-dependent diabetes. Nattrass M, Hale PJ, Eds. London, 1988.
157. Firth RG, Bell PM, Rizza RA. Effects of tolazamide and exogenous insulin on insulin action in patients with non-insulin-dependent diabetes mellitus. New Engl J Med 1986; 314: 1280-1286.
158. Samanta A, Burden AC, Kinghorn A. A comparative study of sulphonylurea and insulin therapy in non-insulin-dependent diabetics who had failed on diet therapy. Diabetes Res 1987; 4: 183-185.

159. Wolffenbuttel BHR, Weber RFA, Verschoor L. A randomized cross-over study of sulfonylurea and insulin treatment in patients with non-insulin-dependent diabetes mellitus failing on diet therapy. Diabetic Med 1989; 6: 520-525.
160. Wolffenbuttel BHR, Weber RFA, Weeks L, Van Koetsveld PM, Verschoor L. Twice daily insulin therapy in patients with type 2 diabetes with secondary failure to sulphonylurea. Diabetes Res 1990; 13: 79-84.
161. Nilsson A, Tideholm B, Kalen J, Katzman P. Incidence of severe hypoglycemia and its causes in insulin-treated diabetics. Acta Med Scand 1988; 224: 257-262.
162. Wolffenbuttel BHR. Combined use of insulin and oral hypoglycaemic agents in the treatment of patients with diabetes mellitus. Eur J Intern Med 1989; 1: 89-95.
163. Bailey TS, Mezitis NHE. Combination therapy with insulin and sulfonylureas for type II diabetes. Diabetes Care 1990; 13: 687-695.
164. Lebovitz HE, Pasmantier R. Combination insulin-sulfonylurea therapy. Diabetes Care 1990; 13: 667-675.
165. Garg A, Grundy SM. Management of dyslipidemia in NIDDM. Diabetes Care 1990; 13: 153-169.
166. Van Deursen RTAM, Nieuwenhuijzen Kruseman AC, Degenaar CP, Wolffenbuttel BHR. De effecten van de cholesterolsyntheseremmer simvastatine bij patiënten met hypercholesterolemie met en zonder diabetes mellitus. Ned Tijdschr Geneeskd 1990; 134: 2142-2146.
167. Winocour PH, Laker MF. Drug therapy for diabetic dyslipoproteinaemia: a practical approach. Diabetic Med 1990; 7: 292-298.
168. Seviour PW, Teal TK, Richmond W, Elkeles RS. Serum lipids, lipoproteins and macrovascular disease in non-insulin-dependent diabetics: a possible new approach to prevention. Diabetic Med 1988; 5: 166-171.
169. Pierce LR. Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy. JAMA 1990; 264: 271-275.
170. Reaven GM, Hoffman BB. A role for insulin in the aetiology and course of hypertension? Lancet 1987; ii: 435-437.
171. Raskin P. How to treat hypertension in diabetic patients. Postgrad Med 1988; 83: 213-232.
172. Lardinois CK, Neuman SL. The effects of antihypertensive agents on serum lipids and lipoproteins. Arch Intern Med 1988; 148: 1280-1288.
173. Ferriere M, Lachmkar H, Richard J-L, Bringer J, Orsetti A, Mirouze J. Captopril and insulin sensitivity. Ann Intern Med 1985; 102: 134-135.
174. Moore MP, Elliott TW, Nicholls MG. Hormonal and metabolic effects of enalapril treatment in hypertensive subjects with NIDDM. Diabetes Care 1988; 11: 397-401.
175. Schoen RE, Frishman WH, Shamoon H. Hormonal and metabolic effects of calcium channel antagonists in man. Am J Med 1988; 84: 492-504.
176. Kingma PJ, Simons JPFHA, Nieuwenhuijzen Kruseman AC, Wolffenbuttel BHR. Calcium entry blockers and their effects on glucose metabolism. Neth J Med 1990; 36: 32-38.
177. Huse DM, Oster G, Killen AR, Lacey MJ, Colditz GA. The economic costs of non-insulin-dependent diabetes mellitus. JAMA 1989; 262: 2708-2713.
178. Alexander WD and South East Thames Diabetes Physicians Group. Diabetes Care in a UK health region: activity, facilities ans costs. Diabetic Med 1988; 5: 577-581.

179. Hortulanus-Beck D, Lefèbvre PJ, Jeanjean MF. Diabetes in the Belgian Province of Luxembourg: frequency, importance of the oral glucose tolerance test and of a fasting glycaemia discretely increased. Diabete & Metabolisme 1990; 16: 311-317.
180. Stuurgroep Toekomstscenario's Gezondheidszorg. Chronische ziekten in het jaar 2005. Deel 1: Scenario's over diabetes mellitus 1990-2005. Bohn, Scheltema & Holkema, Utrecht, 1990.

CHAPTER 2

Clinical characteristics of patients with type 2 diabetes treated in a hospital outpatient-clinic

Treatment, metabolic derangements, late complications

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Submitted

SUMMARY

In order to attain more information on the quality of metabolic control and presence of secondary complications in type 2 diabetic patients treated in a hospital outpatient-clinic, we held a survey among a nonselect sample of 124 of our diabetic patients (56 males, 68 females, mean age 65 ± 11 years, median duration of diabetes 9 (range 1-32) years. The presence of diabetic complications was assessed by specific questionnaires and detailed physical examination. In the 9 diet-treated patients, metabolic control was near-normal (HbA_{1c} 6.3 ± 0.7%), whereas HbA_{1c} levels were higher in patients treated with oral hypoglycaemic agents (7.9 ± 1.3%, n=56), with insulin (8.0 ± 1.5%, n=36) or with insulin combined with oral agents (8.6 ± 1.8%, n=23). Plasma cholesterol and triglyceride levels tended to be lower in the insulin-treated patients. The prevalence of vascular abnormalities was high: 48% of patients had complaints or signs indicating coronary artery disease, 56% had hypertension, 15% cerebrovascular disease and 35% signs of peripheral artery disease. Retinopathy was present in 35 patients (28%), of whom 18 had received lasercoagulation treatment. Microalbuminuria was found in 31 patients (25%), overt proteinuria in 18 patients (14%). The use of cardiovascular medication was high: 57 patients used antihypertensive therapy (of whom 24 a beta-blocking and 20 a calcium entry blocking drug), 37 used diuretics, and 26 long-acting nitrates. Only 25 patients took no medication in addition to their diabetes therapy. The presence of microalbuminuria and proteinuria was a strong indicator for cardiovascular disease, polyneuropathy and retinopathy. In comparison with a population of patients treated by their family physician more of our patients were treated with insulin (48% *vs.* 24%, $p<0.01$). In addition, they showed a higher prevalence of hypertension (56% *vs.* 38%), coronary artery disease (48% *vs.* 40%), and cerebrovascular disease (15% *vs.* 6%). This study confirms the clustering of risk factors for cardiovascular disease in type 2 diabetes mellitus, indicating the need for both optimal blood glucose control and adequate treatment of hypertension and dyslipidaemia.

INTRODUCTION

Secondary complications are frequently observed in patients with type 2 diabetes mellitus (1). Estimations of the prevalence of the various complications differ considerably between studies. This is caused by several factors such as poor definition of the disease state, bias in the selection of patients (hospital-based surveys against patients belonging to the practice of a general practitioner), and differences in the tools or devices that are used to assess the presence or absence of a complication.

The role of diabetes as an independent risk factor for cardiovascular disease is well established (2-5). In type 2 diabetic patients, a two- to three-fold increase of morbidity and mortality attributed to coronary heart disease (CHD) is demonstrated. A comparable increased occurrence of peripheral vascular disease was demonstrated (6-11). Microvascular abnormalities can be found in a considerable number of patients. Retinopathy is observed in 12 to 44% of diabetic patients 10 years after diagnosis (12-15). Diabetic nephropathy is less frequently (0-15%) found in type 2 compared to type 1 diabetic patients (16,17).

A number of risk factors for CHD can be demonstrated in diabetic patients. Twenty to 50% of them suffer from hypertension (18,19). Lipid abnormalities, comprising elevations of both LDL-cholesterol and VLDL-triglycerides, as well as decreases in the levels of HDL-cholesterol (20-22) are reported to occur in at least 30% of patients (23,24). In diabetic patients, elevated triglyceride levels seem to be an independent risk factor for the development of macrovascular disease.

In the Netherlands, only few data are available concerning the occurrence of late complications in type 2 diabetic patients. The present survey was undertaken to characterize the treatment, degree of metabolic (de)compensation and presence of late complications in a cohort of type 2 diabetic patients, treated in the out-patient clinic of a large teaching hospital. Where possible, this cohort of patients is compared with a recently published survey of patients belonging to the practices of four general practitioners (25).

MATERIALS AND METHODS

Patients

From the 940 patients with type 2 diabetes mellitus, who regularly attend the outpatient-clinic of the Department of Internal Medicine of the University Hospital Maastricht, a sample of 124 patients, who consecutively visited the

clinic in a three-week period, was drawn. Patients attending our clinic are for 95% residing in the most south-eastern part of The Netherlands, within a defined geographic area occupied by approximately 200.000 inhabitants.

Previous medical events, present well-being and complaints, presence of specific complaints related to secondary complications (vascular, nephrologic, ophthalmologic), and concomitant use of medication were recorded. Data of routine physical examination, including height (cm), body weight (kg), blood pressure, heart rate, vascular abnormalities, and neurologic examination (tendon reflexes, vibration sense at the medial malleolus and the dorsal aspect of the big toe, and presence of sensory disturbances in the lower extremity) were collected.

Methods

Blood pressure

Systolic and diastolic (Korotkov V) bloodpressure were measured with a standard sphygmomanometer with the patient in the supine position and one minute after standing. The presence of hypertension was scored positive, when a patient was treated with antihypertensive drugs, or when on two repeated occasions after the initial measurement systolic blood pressures above 170 mmHg or diastolic blood pressures equal to or of above 95 mmHg were noted.

Coronary heart disease (CHD)

Four questions to assess the presence of ischaemic heart disease were asked (appendix), which were in part derived from the Rose questionnaire (26). The electrocardiogram was assessed for the presence of definite or probable ischaemia.

Cerebrovascular disease

Questions related to previous cerebrovascular events were asked.

Peripheral vascular disease (PVD)

Four questions exploring the presence of PVD were posed. Peripheral vascular pulsations were recorded by palpation of the dorsal pedal and posterior tibial artery. Peripheral vascular disease was defined as complaints of intermittent claudication, absence of two or more pedal arteries, or amputations made necessary by vascular causes.

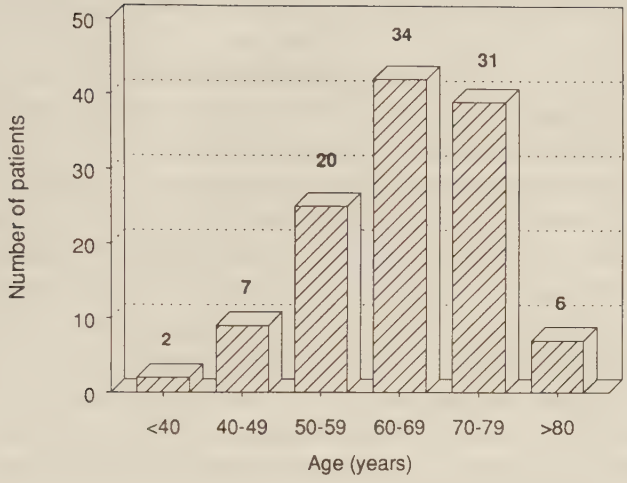


Figure 1. Age distribution of all 124 patients. Data shown above the bars indicate the percentage of patients in a certain subgroup. Thirty-six patients (29%) were younger than 60 years. Age distribution was the same for males and females.

Neuropathy

Neuropathy was scored as: 0. none; 1. complaints, suggestive for peripheral neuropathy, based on the criteria by Boulton (27); 2. decreased vibration sense or signs of sensory disturbances without complaints; 3. sensory complaints and reduced vibration sense or sensory defects.

Retinopathy

Eye examination was performed by the ophthalmologist. Visual acuity was assessed with the use of a Snellen chart. Fundoscopy was carried out after dilation of the pupils. Retinopathy was scored as: 0. none; 1. background; 2. exsudative or preproliferative, but lasercoagulation not yet performed; 3. lasercoagulation performed.

Laboratory determinations

Blood glucose control was assessed by fasting blood glucose, serum fructosamine and glycosylated haemoglobin (HbA_{1c}). In addition, serum creatinine and lipids (cholesterol, HDL-cholesterol and triglycerides), and the presence of microalbuminuria or proteinuria in the first urine voided after waking up on two consecutive days were determined.

Fasting blood glucose was measured in venous whole blood with an automated hexokinase method. Serum fructosamine was determined according to Johnson *et al.* (28) after alkalinising and reduction with nitroblue tetrazolium (Sigma) on the Cobas Bio analyser. Calibration was performed with 1-desoxy-1-morfolinofructose (Sigma) in an albumin solution. The reference values of this assay were lower than those of the commercially-available Fructosamin Roche kit, due to the use of a different standard and reductor. Comparison with the Roche kit was excellent ($r=0.98; y=1.16x+2, p<0.001$). Between-assay coefficient of variation of our fructosamine determination is 4%. HbA_{1c} was determined with high pressure liquid chromatography (DIAMAT, Bio-Rad Laboratories, Richmond, Ca., USA). Normal values are 4.4-6.2%, between-assay cv is 2.6%. Serum creatinine was determined by the Jaffé method. Total cholesterol and triglycerides (TG) were measured with enzymatic methods, HDL-cholesterol was measured after precipitation of VLDL and LDL with polyethyleneglycol 6000. LDL-cholesterol was calculated from the Friedewald formula (LDL-cholesterol = total chol - HDL-chol - 0.45 x TG). Urinary albumin was determined by nephelometry in the first morning urine sample and considered elevated when the albumin/creatinine ratio was above 3.0 mg/mmol. Overt proteinuria (macroalbuminuria) was defined as urinary albumin concentration of >200 mg/l.

ECG's were grouped according to the results of Minnesota coding: 1) coronary heart disease probable: major Q waves or complete left bundle branch block (Minnesota codes 1-1, 1-2, 7-1); 2) coronary heart disease possible: ST-segment abnormalities accompanied by abnormal T-waves, or minor Q/QS wave changes (Minnesota codes 1-3, or any of 4-1, 4-2, 4-3, if accompanied by 5-1 or 5-2 or 5-3); 3) coronary heart disease unlikely (all other Minnesota codes).

Statistical analyses

All data are expressed as means ± SD, or median and range, when not normally distributed. Calculations were performed with the SPSS/PC+ version 3.1 statistical software package (SPSS Inc, Chicago, IL, USA). Differences between group means were tested with one-way analysis of variance. Student-Newman-Keuls test was applied to correct for multiple comparisons. When data were not normally distributed, Kruskal-Wallis analysis of variance was used. For categorical parameters Fisher's exact test (two-sided) was used. Correlations were tested by linear regression analysis. P values < 0.05 were considered statistically significant.

RESULTS

Of the 124 patients, 56 were males and 68 females. Mean (± SD) age was 65 ± 11 years, mean body mass index was 27.7 ± 4.8 kg/m^2. Sixty-two patients were obese (BMI >27.0 kg/m^2). Median known duration of diabetes was 9 years (range 1-32 years). Distribution of the various treatments of diabetes is depicted in table 1. A similar number of obese patients is treated with insulin, compared to normal-weight patients. Variables of blood glucose control were identical in males compared to females. Only in female patients, total plasma cholesterol (6.6 ± 1.2 *vs.* 6.1 ± 1.1 mmol/l, p=0.024) and HDL-cholesterol (1.20 ± 0.37 *vs.* 1.03 ± 0.27 mmol/l, p=0.008) were significantly higher than in males.

The results concerning blood glucose control and lipid variables in the different treatment groups are listed in table 2. In diet-treated patients, HbA_{1c} was 6.3 ± 0.7%, implying that metabolic control was near-normal. In the patients treated with insulin, levels of fasting blood glucose and HbA_{1c} were slightly higher compared to diet- and tablet-treated patients, whereas cholesterol and triglyceride levels tended to be lower. The duration of insulin therapy averaged 2 years, with a range from 1 month to 22 years. Twelve patients used insulin therapy for less than 6 months, and had therefore not yet reached stable metabolic control. HbA_{1c} was 7.9 ± 1.2% in the patients who were on insulin for longer than 1 year, against 8.6 ± 2.0% in the patients who recently had switched to insulin.

Patients in acceptable (HbA_{1c}<8.0%, n=75) and poor control (HbA_{1c} >8.0%, n=49) were similar with regards to body mass index, systolic and diastolic blood pressure, plasma creatinine, total and HDL-cholesterol and triglycerides, and degree of proteinuria. Obese patients had slightly higher diastolic blood pressure (83 ± 9 *vs.* 80 ± 9 mmHg, p=0.04), total cholesterol (6.6 ± 1.1 *vs.* 6.2

Table 1. Treatment of the 124 patients studied.

	All patients	BMI < 27.0	BMI > 27.0
Diet	9	3	6
Sulphonylurea	37	23	14
Biguanides	1	0	1
Sulphonylurea + biguanides	18	6	12
Insulin	36	19	17
Insulin + sulphonylurea	23	11	12

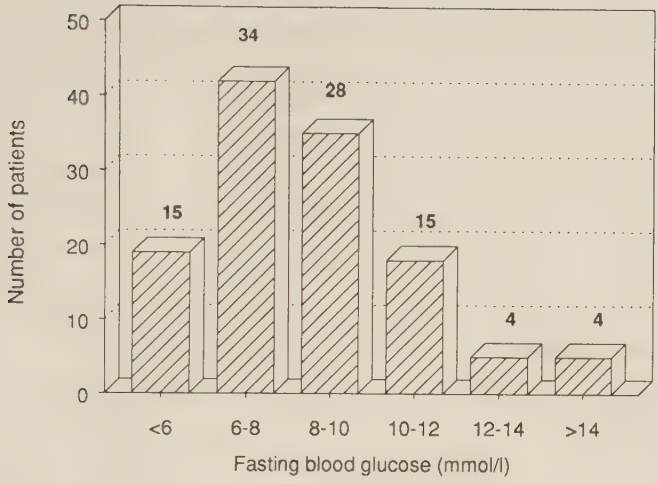
± 1.3 mmol/l, p=0.085), and triglycerides (2.65 ± 1.54 *vs.* 1.91 ± 1.23 mmol/l, p=0.0048).

Data related to the presence of micro- and macrovascular complications in the different treatment groups are depicted in table 3. Hypertension (56%), coronary heart disease (48%) and peripheral vascular disease (35%) were the most prevalent accompanying disturbances. Based on the criteria for hypertension, as described in the Methods Section, three new cases of hypertension were identified. Thirty-one patients (25%) had microalbuminuria, and 18 (14%) manifest proteinuria. Besides a slightly higher prevalence of microalbuminuria in insulin-treated patients, no differences in accompanying problems were observed between diet- or tablet-treated and insulin-treated patients.

Table 2. Characteristics of the 124 patients studied.

	Diet	Oral agents	Insulin	Ins.+OHA
Number of patients	9	56	36	23
Average age (years)	60 ± 12	64 ± 11	65 ± 11	67 ± 9
Known duration	2*	8.5	9.5	10
of diabetes (years)	(1-16)	(1-30)	(1-32)	(1-27)
Sex ratio (F/M)	3/6	31/25	19/17	15/8
Body mass index (kg/m^2)	29.5 ± 6.0	27.7 ± 4.9	26.6 ± 3.7	28.8 ± 5.4
Fasting blood glucose (mmol/l)	6.5 ± 1.3*	8.3 ± 2.3	8.1 ± 3.0	9.0 ± 2.7
Glycosylated haemoglobin (%)	6.3 ± 0.7*	7.9 ± 1.3	8.0 ± 1.5	8.6 ± 1.8
Serum fructosamine (mmol/l)	1.12 ± 0.20*	1.40 ± 0.20	1.40 ± 0.26	1.49 ± 0.32
Total cholesterol (mmol/l)	6.9 ± 1.8	6.5 ± 1.1	6.4 ± 1.2	6.0 ± 1.1
HDL-cholesterol (mmol/l)	1.05 ± 0.34	1.09 ± 0.32	1.16 ± 0.38	1.16 ± 0.33
Triglycerides (mmol/l)	2.77 ± 1.89	2.33 ± 1.60	2.21 ± 1.27	2.05 ± 1.00
LDL-cholesterol (mmol/l)	4.10 ± 1.52	4.43 ± 1.01	4.26 ± 0.95	3.92 ± 0.75
Systolic blood pressure (mmHg)	150 ± 20	150 ± 19	147 ± 18	152 ± 19
Diastolic blood pressure (mmHg)	82 ± 10	82 ± 10	82 ± 9	80 ± 9
Serum creatinine (µmol/l)	88 ± 19	88 ± 22	91 ± 27	87 ± 16

Data as mean ± SD, or median (range); OHA = oral hypoglycaemic agents;
* $p<0.05$ *vs.* tablet- and insulin-treated patients



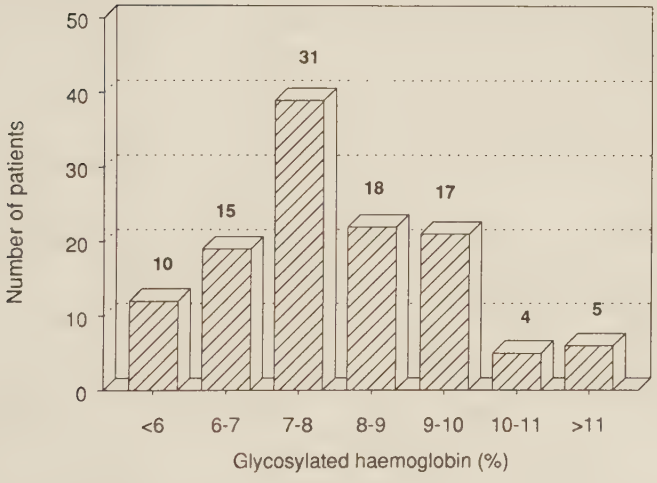


Figure 2. Distribution of fasting blood glucose and glycosylated haemoglobin (HbA_{1c}) in all 124 patients. Data shown above the bars indicate the percentage of patients in a certain subgroup.

Antihypertensive agents were used by 57 (46%) of the patients; 10 of them took a combination of 2 or more drugs (table 4). When the use of antihypertensive agents, diuretics and anti-anginosal therapy was combined, 83 patients (67%) took medication that was prescribed for a reason related to a cardiovascular abnormality (hypertension, angina pectoris, congestive heart failure). Twenty-five patients took no medication in addition to their specific diabetes therapy.

Table 3. Characteristics of patients: secondary complications.

	Diet/ oral agents (n=65)	Insulin (n=59)	All patients (n=124)
Retinopathy			
- background	4	6	10
- exsudative/preproliferative	10	15	25
of whom lasercoagulation	8	10	18
Macroangiopathy			
- angina pectoris (a.p.)	24	23	47
- myocardial infarction (a.m.i.)	13	14	27
- a.p. + a.m.i.	26	25	51
- E.C.G.: definite ischaemia	14	13	27
possible ischaemia	15	20	35
- cerebrovascular accident	9	9	18
- hypertension	38	31	69
- peripheral vascular disease	21	22	43
- amputations	3	4	7
Nephropathy			
- microalbuminuria	11	20*	31
- overt proteinuria	9	9	18
- serum creatinine >120 μmol/l	5	5	10
Neuropathy			
- peripheral polyneuropathy score 1	1	4	5
score 2	7	5	12
score 3	22	23	45

* $p<0.05$ *vs.* tablet-treated patients

Table 5 lists the metabolic control and presence of complications in the patients with different levels of albumin excretion (normo-, micro- or macroalbuminuria). Patients with albuminuria had slightly longer duration of diabetes, and were generally older. Compared to the normoalbuminuric group blood glucose control was slightly worse in the microalbuminuric, but not in the macroalbuminuric group, whereas lipid levels were comparable. With progression from normo- to macroalbuminuria, higher levels of blood pressure and serum creatinine were found, as well as higher prevalence of (treated) hyperten-

Table 4. Characteristics of patients: concomitant medication.

	Diet/ oral agents (n=65)	Insulin (n=59)	All patients (n=124)
Antihypertensive agents	32	25	57
- one drug	26	21	47
of whom + diuretics			21
- two drugs	4	4	8
of whom + diuretics			4
- three drugs	2	0	2
class of antihypertensive agent			
- beta blockers	13	11	24
- calcium entry blockers	10	10	20
- ACE-inhibitors	13	5	18
- vasodilators	0	2	2
- others	2	1	3
Diuretics	18	19	37
Anticoagulant therapy	14	14	28
- coumarines			12
- aspirin			15
- dipyridamol			4
Digoxin	7	8	15
Long-acting nitrates	9	17*	26
Lipid lowering agents	1	5	6

* $p<0.05$ *vs.* diet/tablet-treated patients

sion, peripheral vascular disease, polyneuropathy and retinopathy. The prevalence of coronary heart disease was the same in the three groups.

When our data in hospital-treated patients were compared to a recent survey of patients, belonging to the practices of four general practitioners (25), more of our patients were treated with insulin (48% *vs.* 24%, table 6), whereas the prevalence of hypertension, coronary heart disease and cerebrovascular disease was higher. No differences in peripheral vascular disease or proteinuria was found.

Table 5. Characteristics and observations in the 124 type 2 diabetic patients subdivided by albumin excretion rate.

	Normo albuminuria (n=75)	Micro albuminuria (n=31)	Macro albuminuria (n=18)	
Female/male	43/32	17/14	8/10	
Age (years)	62 ± 11	69 ± 10*	67 ± 9	
Duration (years)	5 (1-32)	11 (1-28)*	12 (2-30)*	
Body mass index (kg/m^2)	27.8 ± 5.1	27.3 ± 4.1	28.2 ± 4.6	
Fasting blood glucose (mmol/l)	8.0 ± 2.6	8.8 ± 2.3*	8.6 ± 3.7	
HbA1c (%)	7.7 ± 1.3	8.4 ± 1.6*	8.4 ± 2.0	
Cholesterol (mmol/l)	6.4 ± 1.2	6.3 ± 1.1	6.7 ± 1.1	
Triglycerides (mmol/l)	2.05 ± 1.12	2.78 ± 1.95	2.36 ± 1.42	
HDL-cholesterol (mmol/l)	1.16 ± 0.36	1.08 ± 0.31	1.07 ± 0.27	
Blood pressure (mmHg)				
systolic	146 ± 17	151 ± 21	159 ± 17*	
diastolic	81 ± 9	80 ± 9	85 ± 10*	
Serum creatinine (μmol/l)	84 ± 20	93 ± 23	98 ± 28*	
Presence of:				
Hypertension	33 (44%)	21 (68%)	15 (83%)	$x^2(2)=11.5$, p=0.0031
Coronary heart disease#	37 (49%)	14 (45%)	8 (44%)	$x^2(2)=0.24$, p=0.89
Cerebrovascular disease	7 (9%)	6 (19%)	5 (28%)	$x^2(2)=4.76$, p=0.093
Peripheral vascular disease	14 (19%)	18 (58%)	11 (61%)	$x^2(2)=21.5$, p=0.000
Peripheral polyneuropathy	30 (40%)	18 (58%)	14 (78%)	$x^2(6)=12.1$, p=0.06
Background retinopathy	4 (6%)	3 (10%)	3 (18%)	
Exsudative retinopathy	8 (11%)	9 (29%)	8 (47%)	$x^2(4)=17.0$, p=0.0019

Data as mean ± SD, or median (range);

* p<0.05 *vs.* normoalbuminuria;

angina pectoris + myoc.infarction + Minnesota code group 1

Table 6. Comparison of the 124 hospital-clinic patients with patients treated by their family physician.

	Hospital	G.P.
Number of patients	124	137
Age (years)	65 ± 11	69 ± 11
Male/female	56/68	53/84
Body mass index (kg/m^2)	27.7 ± 4.8	27.6 ± 4.5
Known duration diabetes	9 (1-32)	7.5 (0.5-40)
Number of patients with diet/oral agents/insulin	9/56/59	23/84/30
Fasting blood glucose (mmol/l)	8.3 ± 2.7	10.8 ± 3.9
Glycosylated haemoglobin (%)	8.0 ± 1.5[a]	8.9 ± 2.9[b]
Serum creatinine (µmol/l)	89 ± 22	92 ± 67
Total cholesterol (mmol/l)	6.4 ± 1.2	6.7 ± 1.3
HDL-cholesterol (mmol/l)	1.12 ± 0.34	1.3 ± 0.6
Triglycerides (mmol/l)	2.28 ± 1.43	2.2 ± 1.5
Systolic blood pressure	149 ± 19	149 ± 18
Diastolic blood pressure	81 ± 9	86 ± 9
Use of antihypertensive agents	57 (46%)	41 (30%)
Number of patients on diuretics	37 (29%)	43 (31%)
Presence of:		
Hypertension	69 (56%)	53 (38%)
Coronary heart disease	59 (48%)[#]	54 (40%)[##]
Cerebrovascular disease	18 (15%)	8 (6%)
Peripheral vascular disease	43 (35%)	71 (52%)
Amputations	7 (6%)	1 (1%)
Proteinuria >500mg/24h	16 (13%)	22 (16%)

[#] angina pectoris + myoc.infarction + Minnesota code group 1;
[##] idem + Minnesota code group 2;
[a] normal values 4.2-6.2% (HPLC-method);
[b] normal values 3.5-5.5% (affinity chromatography)

DISCUSSION

In this hospital-based survey, the majority of type 2 diabetic patients was treated with oral agents or insulin in adjunct to their dietary advices. Their metabolic control was however not adequate. Mean glycosylated haemoglobin of all patients was 8.0%, which was higher in the tablet- and insulin-treated patients. In part this is caused by the difficulties to obtain adequate blood glucose control in type 2 diabetic patients (29): inadequate metabolic control is often the reason for referral by the general practitioner to an internist or endocrinologist. In addition, a considerable number of our patients had been treated with insulin for only a short period, and therefore had not yet reached stable metabolic control. In agreement with the European Consensus (30) we consider a patient eligible for insulin therapy, when his HbA_{1c} level repeatedly exceeds 8.0% despite maximal doses of oral hypoglycaemic agents.

In comparison with a recently published survey of type 2 diabetic patients belonging to the practices of 4 general practitioners in a rural area in the east of the Netherlands (25), a larger number of our patients (48% *vs.* 22%) was treated with insulin. With this more difficult therapy metabolic control was better. Extrapolating from the data of Verhoeven (25) this means that one quarter of the Dutch type 2 diabetic patients are being treated with insulin. In addition, again based on the data of Verhoeven (25) and those of Jonker (31), at least 20% of patients treated by their G.P.'s show such poor metabolic control that they should be treated with insulin. Organisation of diabetes care is very important in this respect; routine care in general practice for type 2 diabetic patients was shown to be less satisfactory than care by the hospital clinic (32). Institution of general practice mini-clinics improved regular review and screening for complications compared to routine care in the general practices (33).

The prevalence of vascular abnormalities in our patients was slightly higher than that reported in the G.P. population. This high prevalence of coronary artery disease (48%), hypertension (56%), cerebrovascular disease (15%) and peripheral artery disease (35%) implies a tendency for clustering of more complicated patients with type 2 diabetes in a hospital-clinic. This may be caused by the necessity of more aggressive treatment after vascular problems have been diagnosed, for instance the institution of insulin therapy because of diabetic foot problems, or worsening of control after myocardial infarction. Otherwise, patients in poor control are likely to be referred by their G.P. for treatment advice and insulin therapy.

In general, a two- to three-fold increase of morbidity and mortality attributed to coronary heart disease is demonstrated in diabetic patients over 45 years of age compared with the non-diabetic population (34). The prevalence of CHD is

already 3 times elevated in newly-diagnosed non-insulin-dependent diabetes as compared with control subjects (35), and may be as high as 30-40% among patients with longer term diabetes (1). More than 40% of our patients suffered from coronary artery disease.

Peripheral vascular disease (PVD) is often found in diabetic patients compared to non-diabetic individuals. Peripheral vascular disease is evidenced by the presence of intermittent claudication, absence of dorsalis pedis pulse, or arterial calcification. Sequelae may be serious infections or ulcers, gangrene and amputation (36). The presence of PVD has been shown to predispose for acute cardiovascular events, such as myocardial infarction and stroke. The vessels most frequently involved are those below the knee, while the occlusions are often multisegmental. The reported incidence and prevalence figures vary because of differences in definition of PVD, the type of diabetes in the patients studied, their age, and diabetes treatment. It is estimated that 6-10% of type 2 diabetic patients have evidence of PVD at the moment of diagnosis, while after 20 years of diabetes this figure averages 45% (or even higher among smokers). Other studies (37) give even higher prevalence figures: absence of ≥ 2 peripheral vascular pulses was noted in 60% of the diabetic patients between 60 and 79 years, against 40% in the non-diabetic individuals. In our patients, these results are less outspoken. This may be due to a lower mean age of our patients; 30% was younger than 60 years. Further, non-invasive techniques such as Doppler studies may considerably increase the number of patients identified to have vascular abnormalities. These investigations are not routinely used for the follow-up of diabetic patients, and usually only performed during evaluation of patients for intermittent claudication, leg ulcers e.a. Although in 7 patients an amputation was performed, in 3 of them this was the consequence of an infectious problem.

Prevalence of hypertension was 54% in the male and 58% in the female patients. Teuscher *et al* (38) reported a hypertension prevalence of 34% in patients with late-onset (after the age of 30 years) diabetes, who were under treatment by their primary care physician. Sprafka *et al* (19) found a prevalence of physician-defined hypertension in 34% of male and 57% of female patients with type 2 diabetes.

Especially in the patients with elevated urinary albumin excretion a higher prevalence of hypertension, cerebrovascular and peripheral vascular disease and retinopathy was found in comparison to normoalbuminuric patients. This is in agreement with other reports. Allawi and Jarrett (39) demonstrated higher blood pressure levels in type 2 diabetic patients with overnight albumin excretion rate 10 μg/min in comparison with patients with lower albumin excretion. Marshall and Alberti (40) found a significant relation between albumin excre-

tion and systolic blood pressure and retinopathy and peripheral vascular disease, whereas others demonstrated increasing albumin excretion in patients with increasing severity of retinopathy (41). Proteinuria and albuminuria are strongly associated with mortality (42,43,44). Therefore, determination of microalbuminuria may identify patients with high risk of acute cardiovascular events, and form a basis for more aggressive therapeutic interventions (normalization of elevated blood pressure and cholesterol levels) to prevent such complications.

It has previously been shown that diabetic patients with hypercholesterolaemia are at very high risk of developing coronary heart disease (24) and dying from cardiovascular causes (44) in comparison to non-diabetic subjects and diabetic subjects with normal cholesterol levels. During a follow-up period of 7 years, the incidence of coronary heart disease was 28% in diabetic patients with serum cholesterol above 7.3 mmol/l against 5% in the diabetics with cholesterol levels below 5.5 mmol/l. The corresponding figures for non-diabetic men were 9.4% and 2.4%, respectively. Similar data are reported from the Prospective Cardiovascular Münster (PROCAM) study (23). In our survey, total and LDL-cholesterol were considerably higher, and HDL-cholesterol was lower compared to non-diabetic individuals. Furthermore, although metabolic control was good in the diet-treated patients, they tended to have higher total cholesterol and triglyceride levels, and lower HDL-cholesterol compared to insulin-treated patients. Considering the high prevalence of cardiovascular disease these findings reappraise the tremendous impact of hypercholesterolaemia as a risk factor in diabetic patients, and urges for extensive efforts to normalize serum cholesterol (45).

Due to the presence of severe complications use of medication in addition to the specific antidiabetic therapy is very frequent. Antihypertensive or anti-anginosal agents are being used by almost 50% of the patients. Sixty-seven percent of the patients take medication that is prescribed for a reason related to a cardiovascular abnormality. This number is quite similar to that of other reports (25,46). Only 25 patients take no additional medication at all. Twenty percent of the patients used beta-blockers, and 30% took diuretics. Both types of drugs have deleterious effects on glucose and lipid metabolism: they may worsen blood glucose control, and elevate cholesterol and triglyceride levels (47,48). Further, beta-blockers may impair the recognition of and recovery from hypoglycaemia, which risk is more substantial in insulin-treated patients. As ACE-inhibitors and calcium-entry blockers show less or no negative metabolic effects (49), these are considered at present the first-line antihypertensive agents in diabetic patients.

We conclude that the occurrence of vascular abnormalities is high in patients with type 2 diabetes mellitus, both among the patients of our hospital outpatient-clinic, as well as in the patients in the general practice. The demonstration of microalbuminuria already is a strong indicator for such complications. Considering the apparent clustering of risk factors as poor metabolic control, obesity, hypertension and dyslipidaemia, attaining optimal blood glucose control forms only one of the aims of treatment in order to prevent life-limiting vascular complications. Striving for normal HbA_{1c} levels seems futile without concomitant adequate treatment of elevated blood pressure and hypercholesterolaemia.

REFERENCES

1. Panzram G. Mortality and survival in type II (non-insulin-dependent) diabetes mellitus. Diabetologia 1987; 30: 123-131.
2. Jarrett RJ. Epidemiology and public health aspects of non-insulin-dependent diabetes mellitus. Epidemiol Rev 1989; 11: 151-171.
3. Keen H, Jarrett RJ, Fuller JH, McCartney P. Hyperglycaemia and arterial disease. Diabetes 1981; 30 (suppl.): 49-53.
4. Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4400 patients observed between 1947 and 1973. Diabetes Care 1978; 1: 168-188 and 252-263.
5. Brand FN, Abbott RD, Kannel WB. Diabetes, intermittent claudication, and risk of cardiovascular events the Framingham study. Diabetes 1989; 38: 504-509.
6. Kannel WB. Lipids, diabetes and coronary heart disease: insights from the Framingham Study. Am Heart J 1985; 110: 1100-1107.
7. Fuller JH, Shipley MJ, Rose G, Jarrett RJ, Keen H. Mortality from coronary heart disease and stroke in relation to degree of glycaemia: the Whitehall study. Br Med J 1983; 287: 867-870.
8. Greene DA. Acute and chronic complications of diabetes mellitus in older patients. Am J Med 1986; 80 (suppl. 5a): 36-53.
9. Kreines K, Johnson E, Albrink M, *et al.* The course of peripheral vascular disease in non-insulin-dependent diabetes. Diabetes Care 1985; 8: 235-243.
10. Beach KW, Bedford GR, Bergelin RO. Progression of lower arterial occlusive disease in type II diabetes mellitus. Diabetes Care 1988; 11: 464-472.
11. Abbott RD, Brand FN, Kannel WB. Epidemiology of some peripheral arterial findings in diabetic men and women: experiences from the Framingham study. Am J Med 1990; 88: 376-381.
12. Blankenship GW, Skyler JS. Diabetic retinopathy: a clinical survey. Diabetes Care 1978; 1: 127-131.
13. Chase HP, Jackson WE, Hoops SL, *et al.* Glucose control and the renal and retinal complications of insulin-dependent diabetes. JAMA 1989; 261: 1155-1160.

14. Hiller R, Sperduto RD, Podgor MJ, Ferris FL, Wilson PWF. Diabetic retinopathy and cardiovascular disease in type II diabetics. The Framingham heart study and the Framingham eye study. Am J Epidemiol 1988; 128: 402-409.
15. Klein R, Klein BEK, Moss SE, Davis MD, De Mets DL. The Wisconsin Epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy, when age at diagnosis 30 or more years. Arch Ophthalmol 1984; 102: 527-532.
16. Selby JV, FitzSimmons SC, Newman JM, Katz P, Sepe S, Showstack J. The natural history and epidemiology of diabetic nephropathy implications for prevention and control. JAMA 1990; 263: 1954-1960.
17. Cooper ME, Frauman A, O'Brien RCO, Seeman E, Murray RML, Jerums G. Progression of proteinuria in type 1 and type II diabetes. Diabetic Med 1988; 5: 361-368.
18. Klein R, Klein BEK, Moss SE, Demets DL. Blood pressure and hypertension in diabetes. Am J Epidemiol 1985 122: 75-89.
19. Sprafka JM, Bender AP, Jagger HG. Prevalence of hypertension and associated risk factors among diabetic individuals. The Three-City Study. Diabetes Care 1988; 11: 17-22.
20. Uusitupa M, Siitonen O. The relationship of cardiovascular risk factors to the prevalence of coronary heart disease in newly diagnosed type II (non-insulin-dependent) diabetes. Diabetologia 1985; 28: 653-659.
21. Reaven GM. Abnormal lipoprotein metabolism in non-insulin-dependent diabetes mellitus. Am J Med 1987; 83 (suppl.3A): 31-40.
22. Billingham MS, Milles JJ, Bailey CJ, Hall RA. Lipoprotein subfraction composition in non-insulin-dependent diabetes treated by diet, sulphonylurea, and insulin. Metabolism 1989; 38: 850-857.
23. Assmann G, Schulte H. Diabetes mellitus and hypertension in the elderly: concomitant hyperlipidemia and coronary heart disease risk. Am J Cardiol 1989; 63: 33H-37H.
24. Rosengren A, Welin L, Tsipogianni A, Wilhelmsen L. Impact of cardiovascular risk factors on coronary heart disease and mortality among middle aged diabetic men: a general population study. Br Med J 1989; 299: 1127-1131.
25. Verhoeven S. Treatment, follow-up and metabolic regulation of patients with diabetes mellitus type II and the prevalence of late complications in this group of patients. Thesis, Rotterdam/Heerde, 1989.
26. Rose GA, Blackburn H, Gillum RF, Prineas RJ. Cardiovascular survey methods. 2nd edn. Geneva: World Health Organization, 1982.
27. Boulton AJM, Knight G, Dury J, Ward JC. The prevalence of symptomatic diabetic neuropathy in an insulin-treated population. Diabetes Care 1985; 8: 125-128.
28. Johnson RN, Metcalf PA, Baker JR. Fructosamine: a new approach to the estimation of serum glycosylprotein. An index of diabetic control. Clinica Chim Acta 1982; 127: 87-95.
29. Peacock I, Tattersall RB. The difficult choice of treatment for poorly controlled maturity onset diabetes: tablets or insulin. Br Med J 1984; 288: 1956-1959.
30. Alberti KGMM, Gries FA. Management of non-insulin-dependent diabetes mellitus in Europe: a consensus view. Diabetic Med 1988; 5: 275-281.
31. Jonker JJ, Rozendaal AA. Tweejaars resultaten van het Diabetes Centrum Rotterdam (DCR). Tijdschr Therapie Geneesmiddel Onderzoek 1988; 13: 209-220.
32. Hayes TM, Harries J. Randomised controlled trial of routine hospital clinic care versus routine general practice care for type II diabetics. Br Med J 1984; 289: 728-730.

33. Williams DRR, Munroe C, Hospedales CJ, Greenwood RH. A three-year evaluation of the quality of diabetes care in the Norwich community care scheme. Diabetic Med 1990; 7: 74-79.
34. Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the Framingham study. Circulation 1979; 59: 8-13.
35. Uusitupa M, Siitonen O, Aro A, Pyörälä K. Prevalence of coronary heart disease, left ventricular failure and hypertension in middle-aged, newly diagnosed type 2 (non-insulin-dependent) diabetic subjects. Diabetologia 1985; 28: 22-27.
36. Levin ME, Sicard GA. Peripheral vascular disease in the person with diabetes. In: Ellenberg and Rifkin's Diabetes mellitus: Theory and Practice. Rifkin H, Porte D Jr, Eds. 4th Edition, Elsevier Science Publishing Co., New Hyde Park, NY, 1990.
37. Pyörälä K, Laakso M. Macrovascular disease in diabetes mellitus. In: Mann JI, Pyörälä K, Teuscher K, eds. Diabetes in epidemiological perspective. Churchill-Livingstone, Edinburgh-London, 1983: 183-231.
38. Teuscher A, Egger M, Herman JB. Diabetes and hypertension blood pressure in clinical diabetic patients and a control population. Arch Intern Med 1989; 149: 1942-1945.
39. Allawi J, Jarrett RJ. Microalbuminuria and cardiovascular risk factors in type 2 diabetes mellitus. Diabetic Med 1989; 7: 115-118.
40. Marshall SM, Alberti KGMM. Comparison of the prevalence and associated features of abnormal albumin excretion in insulin-dependent and non-insulin-dependent diabetes. Q J Med 1989; 70: 61-71.
41. Agardh E, Torffvit O, Agardh C-D. Putative risk factors associated with retinopathy in patients with diabetes diagnosed at or after 30 years of age. Diabetic Med 1989; 6: 724-727.
42. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. New Engl J Med 1984; 310: 356-360.
43. Jarrett RJ, Viberti GC, Argyropoulos A, Hill RD, Mahmud U, Murells T. Microalbuminuria predicts mortality in non-insulin-dependent diabetes. Diabetic Med 1984; 1: 17-20.
44. Morrish NJ, Stevens LK, Head J, Fuller JH, Jarrett RJ, Keen H. A prospective study of mortality among middle-aged diabetic patients (the London cohort of the WHO Multinational Study of Vascular Disease in Diabetics) II: associated risk factors. Diabetologia 1990; 33: 542-548.
45. Recognition and management of hyperlipidemia in adults: policy statement of the European Atherosclerosis Society. Eur Heart J 1988; 9: 571-600.
46. Gram J, Damsgaard EM. Drug consumption in elderly diabetics. Diab Res Clin Pract 1989; 7: 293-298.
47. Lardinois CK, Neuman SL. The effects of antihypertensive agents on serum lipids and lipoproteins. Arch Intern Med 1988; 148: 1280-1288.
48. Kaplan NM, Rosenstock J, Raskin P. A differing view of treatment of hypertension in patients with diabetes mellitus. Arch Intern Med 1987; 147: 1160-1162.
49. Kingma PJ, Simons JPFHA, Nieuwenhuijzen Kruseman AC, Wolffenbuttel BHR. Calcium entry blockers and their effects on glucose metabolism. Neth J Med 1990; 36: 32-38.

APPENDIX

General questions

Personal:
- name and sex
- date of birth
- time of diagnosis of diabetes
- diabetes in pregnancy

Other diseases than diabetes mellitus that are known to be present:
- hypertension
- cardiovascular diseases (myocardial infarction, angina pectoris)
- cerebrovascular events
- kidney diseases
- other important complaints and diseases

Use of medication:
- antihypertensive agents
- diuretics
- anticoagulants
- corticosteroids
- other drugs (specified)

Smoking:
- duration and amount

Present therapy of diabetes:
- oral hypoglycaemic agents or insulin
- duration of and dose of treatment

Questions related to ischaemic heart disease:
- are there complaints of chest pain, provoked by exercise or cold?
- was the patient previously been evaluated because of cardiac complaints?
- was there a hospital admittance because of:
  myocardial infarction or
  impending infarction, or
  was cardiac bypass surgery performed?
- does the patient use medication because of cardiac complaints?

Questions related to cerebrovascular disease:
- loss of power or movement in arm or leg, or speech disturbances for a short period of time
- was the patient previously been evaluated because of such complaints?
- carotid artery surgery
- previous cardiac surgery (valve replacement)

Questions related to peripheral vascular disease:
- are there complaints of pain in one or both legs during walking, and does this pain subside when holding still?
- is the walking distance limited because of pain in one or both legs?
- are the any complaints of cold feet?
- was surgery performed on the blood vessels in legs or abdomen?

Questions related to nephropathy:
- are there known diseases of kidney or urinary tract?
- did the patient suffer from kidney stones?
- were there previous urinary tract infections?
- is the patient known to have diabetic nephropathy?
- does the patient have an indwelling bladder catheter?
- any previous surgery to the urinary tract?

Questions related to retinopathy:
- are there problems with seeing?
- hospital admittance because of eye problems: what was the diagnosis and treatment
- use of medication because of eye problems
- known to have other (non-diabetic) eye disease

Questions related to neuropathy:
- peripheral:
  pricking or burning sensations in feet or legs
  complaints present during the day or the night
  can the patient walk longer distances?
  if not: stop walking after what distance
  do small skin wounds heal rapidly?
- autonomic:
  complaints of recurrent diarrhoea
  is there still need to urinate after miction?

Physical examination

General:
- height and length
- blood pressure supine and standing

Vascular examination:
- pulsations (and murmurs) of:
  carotid artery
  femoral artery
  popliteal artery
  posterior tibial artery
  dorsal pedal artery

Neurologic examination:
- loss of muscle strength
- reflexes
- vibration sense

Retinopathy:
- visual acuity
- retinal abnormalities

Inspection of the feet:
- abnormalities of color
- skin abnormalities (edema, nails, infection, small wounds)
- anatomical abnormalities (clawfoot, valgus)

CHAPTER 3

Clinical characteristics and management of diabetic patients residing in a nursing home

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Submitted

SUMMARY

In 38 diabetic patients, chronically admitted to a nursing home, the clinical situation and presence of secondary diabetic complications were assessed, and their macrovascular complications and degree of glycaemic control compared with those in ambulatory diabetic patients, matched for age, sex, known duration of diabetes, and specific antidiabetic therapy. No differences in blood glucose control, plasma triglycerides, blood pressure and serum creatinine were observed between both groups of patients. Plasma cholesterol levels were higher in the ambulatory patients (6.4 ± 1.0 *vs.* 5.6 ± 1.1 mmol/l, p=0.008). Twenty-two nursing home patients had suffered from stroke, against 4 ambulatory patients. Hypertension was found in almost 50% of all patients, whereas its prevalence was the highest in the stroke patients (69 *vs.* 36%, p<0.01). In the nursing home patients peripheral vascular abnormalities, skin necrosis or leg ulcers and recurrent urinary tract infections were frequently encountered, whereas in the ambulatory patients cardiac complaints were more prevalent. Use of medication, especially diuretics and anticoagulant agents, was higher in the nursing home patients. Diabetes and the sequelae of its macrovascular complications may greatly impair the quality of life of the diabetic patient, and place a large financial and personal burden on the health care in general. Better identification of diabetic patients with high risk of stroke is necessary.

INTRODUCTION

Diabetes and its complications may greatly impair the quality of life of the elderly diabetic patient (1), and place a large burden of costs on health care in general. Diabetes is one of the major risk factors for cardiovascular disease. Admission of diabetic patients to a nursing home is often necessary for permanent care or for the purpose of psychological and somatic rehabilitation after a cardiovascular event. Previous studies have indicated that about 15% of patients in nursing homes have diabetes mellitus (2). One-third of them is treated with insulin. The exact reasons for admission to a nursing home may vary considerably. The presence of micro- and macrovascular diabetic complications forms a causative or promoting factor. Diabetic patients in a nursing home show a high prevalence of macrovascular abnormalities, leading to signs and symptoms of coronary, cerebral and peripheral vascular insufficiency, as well as a high prevalence of visual abnormalities, including diabetic retinopathy, maculopathy, and cataract (2,3). Furthermore, a high incidence of infections, both of the skin and of the urinary tract, was reported in such patients (2).

To get an impression about the clinical conditions predisposing for admission to a nursing home, we held a survey among diabetic patients, admitted to a nursing home, to characterize their clinical situation, the presence of secondary macrovascular complications and facilities necessary for the management of these patients. The severity of vascular complications and degree of glycaemic control in these patients were compared with those in ambulatory diabetic patients, carefully matched for age, sex, known duration of diabetes, and specific antidiabetic therapy.

MATERIALS AND METHODS

Patients

Of 55 patients with diabetes mellitus according to the WHO criteria (4), who were chronically admitted to two nursing homes in the city of Maastricht (total population 470 patients), thirty-eight participated in the study. The mean age of the patients was 77 ± 9 (range 58-92) years. There were 9 male and 29 female patients. The clinical characteristics of this group of patients are summarized in table 1. In 17 patients the assessments outlined below were not performed. Reasons for this were the presence of psychogeriatric illnesses, malignancy or diminished life expectancy less than 2 years, or refusal by the patient. Age,

diabetes duration and presence of vascular complications of the latter group was not different from the patients studied.

Assessments

For each patient, the following information was recorded by means of a detailed history, review of the notes of previous hospital admissions and charts from the outpatient clinic, and present nursing home patient charts: the reason for admission to the nursing home, previous illnesses and medical events, presence of secondary diabetic complications (vascular, neurologic, nephrologic) and present medication on prescription (excluding vitamin supplements and laxatives). Data on retinal abnormalities were to limited to allow analysis. Routine physical examination was performed, with special attention for systolic and diastolic (Korotkov V) blood pressures, heart rate, peripheral vascular abnormalities, gangrene and amputations, and neurologic examination (vibration sense, reflexes).

Laboratory evaluation included urine analysis for white cells and protein, serum creatinine, as well as plasma lipid determinations (total cholesterol and triglycerides). Blood glucose control was assessed by determination of glycosylated haemoglobin (HbA_{1c}), serum fructosamine, and fasting blood glucose level. Fasting plasma free insulin and C-peptide levels were measured to determine residual islet B-cell function, and to ascertain type of diabetes. In addition, an electrocardiogram was made.

Comparison with hospital-treated patients

The clinical characteristics and the degree of blood glucose control of the nursing home diabetic patients were compared with a group of elderly ambulatory diabetic patients, matched as closely as possible for age, sex, time from diagnosis of diabetes, and antidiabetic therapy. Those patients were selected from a large group of diabetic outpatients treated in the Department of Internal Medicine of the University Hospital Maastricht.

Laboratory determinations

Blood glucose was measured in venous whole blood with an automated hexokinase method. Serum fructosamine was determined on the Cobas Bio analyser according to Johnson *et al.* (5) after alkalinising and reduction with nitroblue tetrazolium (Sigma). Calibration was performed with 1-desoxy-1-morpholino-fructose (Sigma) in an albumin solution. The reference values of this assay are

lower than those of the commercially-available Fructosamine Roche kit, due to the use of a different standard and reductor. Comparison with the Roche kit was excellent ($r=0.98; y=1.16x+2$, $p<0.001$). Between-assay of our fructosamine determination is 4%. HbA_{1c} was determined with high pressure liquid chromatography (DIAMAT, Bio-Rad Laboratories, Richmond, Ca., USA, normal values 4.4-6.2%, between-assay cv 2.6%). Plasma cholesterol and triglycerides were determined by enzymatic methods. Plasma free insulin (Pharmacia, Uppsala, Sweden) and C-peptide (Mallinckrodt, FRG) levels were measured with radio-immunoassay. Between-assay variation of insulin-RIA was 7.5%, and C-peptide 9%.

The electrocardiogram was assessed for the presence of definite or probable ischaemia according to the Minnesota code (6). Q- and QS-abnormalities (Minnesota codes 1-1, 1-2, 7-1) were considered definite signs of myocardial infarction, minor Q-QS changes (code 1-3) and ST-segment and T-wave abnormalities (Minnesota codes 4-1 through 4-4, if accompanied by 5-1 or 5-2 or 5-3) were considered possible ischaemia.

Statistical analyses

All data are reported as means ± SD. Differences between group means were tested with one-way analysis of variance, with Student-Newman-Keuls correction for multiple comparisons, or by non-parametric test (Wilcoxon), when data were not normally distributed. For variables involving categorical classifications, chi-square and Fisher's exact tests (two-sided) are used. P-values less than 0.05 were considered statistically significant.

RESULTS

The clinical characteristics of both groups of diabetic patients are depicted in table 1. Four nursing home patients were treated with diet alone, whereas 19 received oral hypoglycaemic agents as well. Nine of the nursing home patients received biguanides (metformin), alone (n=3) or in addition to sulphonylurea (n=6). Matching for this therapy was not completely possible, because of the small number of matching ambulatory diabetic patients treated with metformin (n=5). Fifteen nursing home patients used insulin, for a median period of 20 months. Daily insulin dose was 39 ± 15 U. Based on the levels of fasting C-peptide, one nursing home patient was classified as having insulin-dependent (type 1) diabetes.

Table 1. Clinical characteristics of the patients studied.

	NURSING HOME		AMBULATORY	
	Diet and/or oral agents (n=23)	Insulin (n=15)	Diet and/or oral agents (n=22)	Insulin (n=16)
Age (years)	78 ± 8	77 ± 10	77 ± 7	78 ± 9
Male: female	5:18	4:11	6:16	3:13
Body mass index >27 kg/m^2	5	5	8	10
Known duration of diabetes (years)	10 (1.5-30)	13 (1-50)	11 (1-22)	16 (1-32)
Duration of insulin therapy (months)		20 (10-84)		24 (1-108)
Units insulin		39 ± 15		34 ± 13

Mean ± SD, or median (range)

Table 2. Metabolic and bloodpressure data in the nursing home and ambulatory diabetic patients.

	NURSING HOME		AMBULATORY	
	Diet and/or oral agents (n=23)	Insulin (n=15)	Diet and/or oral agents (n=22)	Insulin (n=16)
Fasting blood glucose (mmol/l)	6.2 ± 1.9	9.3 ± 3.7$^{\#}$	8.3 ± 2.2$^{\$}$	8.0 ± 3.1
Serum fructosamine (mmol/l)	1.22 ± 0.18	1.34 ± 0.16	1.47 ± 0.32$^{\$}$	1.42 ± 0.38
Glycosylated haemoglobin (%)	7.3 ± 1.5	8.1 ± 1.3	8.1 ± 1.6	8.2 ± 1.8
Fasting plasma insulin (pmol/l)	62 (30-210)	88 (44-163)	N.D.	N.D.
Fasting plasma C-peptide (pmol/l)	830 (360-2190)	490 (10-2710)*	N.D.	N.D.
Plasma cholesterol (mmol/l)	5.7 ± 1.2	5.4 ± 1.0	6.7 ± 1.0$^{\$}$	6.1 ± 1.0
Plasma triglycerides (mmol/l)	2.00 ± 1.18	1.57 ± 0.88	1.89 ± 0.90	1.60 ± 0.74
Serum creatinine (µmol/l)	89 ± 32	97 ± 46	96 ± 23	92 ± 28
Systolic blood pressure (mm Hg)	154 ± 23	141 ± 21	153 ± 12	148 ± 22
Diastolic blood pressure (mm Hg)	89 ± 11	84 ± 14	80 ± 6$^{\$}$	84 ± 9

* $p<0.05$, $^{\#}$ $p<0.01$ *vs.* tablet-treated nursing home patients;
$^{\$}$ $p<0.01$ *vs.* nursing home patients; N.D. = not determined

Although fasting blood glucose levels were the lowest in the nursing home patients, treated with diet and oral agents, no overall differences in blood glucose control, as determined by serum fructosamine and HbA_{1c}, were observed (table 2). Plasma cholesterol levels were higher in the ambulatory patients (6.4 ± 1.0 *vs.* 5.6 ± 1.1 mmol/l, p=0.008), whereas plasma triglycerides, blood pressure and serum creatinine did not differ.

Table 3 shows the prevalence of the associated medical problems which were found in both groups of patients. No differences were found between diabetic patients treated with oral agents and those on insulin. Prevalence of macrovascular complications, especially cerebrovascular accidents, was extremely high in the nursing home patients. Sixteen patients had suffered an extensive cerebrovascular accident, leading to hemiplegia. In most of the cases this was the reason for admittance to the nursing home. Only 4 ambulatory patients ($p<0.001$) had previously experienced a cerebrovascular problem. The prevalence of previous myocardial infarction or complaints suggesting angina pec-

Table 3. Medical problems in the nursing home and ambulatory diabetic patients.

	NURSING HOME			AMBULATORY		
	Diet and/ or oral agents (n=23)	Insulin (n=15)	Total (n=38)	Diet and/ or oral agents (n=22)	Insulin (n=16)	Total (n=38)
Hypertension	12 (52%)	7 (47%)	19 (50%)	7 (33%)	10 (62%)	17 (45%)
History of myocardial infarction or angina pectoris	6 (26%)	3 (20%)	9 (24%)	12 (57%)*	6 (38%)	18 (47%)*
ECG-changes definite ischaemia[b]	7 (30%)	3 (20%)	10 (26%)	6 (27%)	5 (31%)	11 (29%)
Cerebrovascular accident	15 (65%)	7 (47%)	22 (58%)	0 (0%)&	4 (25%)	4 (11%)&
Peripheral vascular disease						
- peripheral pulses absent	19 (83%)	10 (67%)	29 (76%)	4 (19%)&	9 (56%)	13 (34%)&
- amputations	4 (17%)	5 (33%)	9 (24%)	1 (5%)	4 (25%)	5 (13%)
Overt proteinuria	6 (26%)	4 (27%)	10 (26%)	4 (19%)	3 (19%)	7 (18%)
Microalbuminuria	8 (35%)	4 (27%)	12 (32%)	4 (19%)	4 (25%)	8 (21%)
Urinary tract infections	17 (74%)	12 (80%)	29 (76%)	1 (5%)&	5 (31%)#	6 (16%)&
Urinary bladder catheter	6 (26%)	2 (13%)	8 (21%)	0 (0%)*	0 (0%)*	0 (0%)#

[b] Minnesota codes 1-1, 1-2, 7-1;

* $p<0.05$, # $p<0.01$, & $p<0.001$ *vs.* nursing home patients

Table 4. Use of prescriptional medication in the nursing home and ambulatory patients.

	NURSING HOME			AMBULATORY		
	Diet and/or oral agents (n=23)	Insulin (n=15)	Total (n=38)	Diet and/or oral agents (n=22)	Insulin (n=16)	Total (n=38)
Number of prescription drugs (median, range)	3 0 - 6	3 0 - 11	3 0 - 11	2 0 - 4	1 0 - 7	1 0 - 7
Antihypertensive agents	8 (35%)	5 (34%)	13 (34%)	5 (24%)	3 (18%)	8 (21%)
Diuretic drugs	13 (57%)	8 (54%)	21 (55%)	6 (29%)	6 (35%)	12 (32%)*
Digitalis	5 (22%)	3 (20%)	8 (21%)	3 (14%)	3 (18%)	6 (16%)
Anticoagulant agents[a]	14 (61%)	6 (40%)	20 (53%)	4 (19%)#	1 (6%)*	5 (13%)&

[a] includes acenocoumarol, aspirin and dypiridamol;
* $p<0.05$, # $p<0.01$, & $p<0.001$, *vs.* nursing home patients

toris was lower in the nursing home patients than in ambulatory patients ($p<0.05$). Peripheral arterial disease, as assessed on clinical grounds by palpation of peripheral pulses, was present in 29 nursing home patients. This finding may overestimate the true prevalence of arterial disease, because in 6 patients marked ankle edema was present, which made palpation of the pulses difficult. In 13 patients necrosis or decubitus of the skin at the sacrum or heels was found, and in 9 patients previously amputations were performed (5 patients with toe-amputations, 3 with lower leg and 1 with upper leg amputation). Absence of peripheral pulsations was less prevalent in the ambulatory patients ($p<0.001$). No differences in proteinuria were observed, although the prevalence of proteinuria may be overestimated in the nursing home patients, of whom 8 have permanent urinary bladder catheter, and who experienced more frequent urinary tract infections. The use of medication (diabetes therapy not included) was significantly less in the ambulatory patients. Especially diuretics and anticoagulant therapy were more frequently prescribed in the nursing home patients.

Age, duration of diabetes, number of patients on insulin therapy, blood glucose control and serum lipids were not different, when the 26 patients who had suffered a cerebrovascular event (CVA-group) were compared with the 50 patients without cerebrovascular disease (table 5). The proportion of patients with cardiac complaints or pathologic ECG was slightly, but not significantly smaller in the CVA group. Eighteen of the 26 patients with a CVA were known to have or being treated for hypertension, against 18 of the other group

($p<0.01$); actual blood pressure levels were similar (150/87 *vs.* 149/82 mm Hg). More CVA patients used anticoagulant therapy (15 *vs.* 10 patients, $p<0.001$).

DISCUSSION

The number of patients suffering from diabetes in our nursing home population (12%) was similar to that reported in the literature (2). All but one were diagnosed as having non-insulin-dependent (type 2) diabetes. Forty percent of them was treated with insulin. Most patients were fairly controlled, considering their average HbA_{1c} of 7.6%. Blood glucose control was comparable to that of a group of age-, sex- and therapy-matched diabetic patients, treated at the outpatient-clinic of a large teaching-hospital. Plasma cholesterol levels were higher in the ambulatory patients. This may in part be explained by the slightly higher proportion of obese ambulatory patients, and perhaps the larger number of nursing home patients treated with metformin.

A striking finding in the nursing home patients is the very high prevalence of macroangiopathic complications. This comprises especially cerebrovascular accidents, which were found in 22 of the 38 patients, and peripheral arterial disease, ascertained by physical examination, and present in 29 patients. This finding is not surprising, because such vascular abnormalities may lead to hemiplegia or amputations, decrease daily functioning, and form the main reasons for admittance to the nursing home, either for revalidation or for permanent stay. Surprisingly, the prevalence of coronary artery disease, as estimated from cardiac complaints and use of antianginal medication was lower in the nursing home patients than in the ambulatory patients. This can in part be explained by the limited mobility of the patients; thus, exertional chest pain will seldomly be reported. Secondly, it may be argued that those diabetic patients developing severe coronary atherosclerosis will have died prematurely from myocardial infarction before reaching an elderly age or before developing cerebrovascular complications. Silent ischaemia and silent myocardial infarction are known to be more common in elderly patients (7), and are even more prevalent in diabetic patients due to reduced pain sensations because of neuropathy (8). It is, however, expected that this occurs to the same extent in both the nursing home and the ambulatory patients. Coronary artery disease was more prominent in the ambulatory patients, who had less cerebrovascular and peripheral arterial disease. Coronary heart disease represents the most common form of vascular disease and the most prominent cause of death in type 2 diabetes (9). It may be postulated from our data that macrovascular disease in diabetic patients is expressed in at least two different forms, either as coronary

Table 5. Metabolic data and prevalence of complications in diabetic patients with (n=26) and without (n=50) signs of cerebrovascular abnormalities.

	With CVA (n=26)	Without CVA (n=50)
Fasting blood glucose (mmol/l)	7.8 ± 2.5	7.8 ± 2.9
Serum fructosamine (mmol/l)	1.32 ± 0.25	1.39 ± 0.31
Glycosylated haemoglobin (%)	7.8 ± 1.6	8.0 ± 1.6
Plasma cholesterol (mmol/l)	6.1 ± 1.3	6.0 ± 1.0
Plasma triglycerides (mmol/l)	2.11 ± 1.15	1.64 ± 0.78
Serum creatinine (μmol/l)	92 ± 43	94 ± 24
Syst/diast.blood pressure (mm Hg)	150/87	149/82
Hypertension	18 (69%)[#]	18 (36%)
History of myocardial infarction or angina pectoris	7 (27%)	20 (40%)
Abnormal ECG[b]	5 (19%)	16 (32%)
Peripheral pulses absent	18 (69%)	24 (48%)

[b] Minnesota codes 1-1, 1-2, 7-1; [#] $p<0.01$ *vs.* CVA patients

artery disease, or as peripheral-cerebrovascular abnormalities. In comparison with our data, Mooradian *et al* reported a lower prevalence of cerebrovascular (32%) and peripheral vascular (26%) disease, and a higher prevalence of angina or myocardial infarction (60%) in their study of medical problems in nursing home diabetic patients (3). This discrepancy may in part be caused by methodological differences: their survey was mainly based on clinical history data suggestive of macroangiopathy.

The atherosclerotic process is more common in the diabetic than in the non-diabetic individual, appears at a younger age, and progresses more rapidly (10). It is almost as common in women as in men (11). In diabetic peripheral vascular disease (PVD), the vessels most frequently involved are those below the knee, the tibials and peroneals, and their smaller branches. At time of diagnosis (when hyperglycaemia usually is present for a number of years) 8% of type 2 diabetic patients have evidence of PVD. After 10 years the cumulative incidence averages 30% (11), and after 20 years even 50% (10). In the Framingham study diabetes was associated with a two- to threefold excess risk of intermittent claudication (12). About 50% of nontraumatic amputations are performed on diabetic patients. Stroke occurs two to six times more frequently

in diabetic patients compared with non-diabetic subjects (13). Type 2 diabetic patients show a 2- to 4-fold increase in risk for death from cerebrovascular disease compared to non-diabetic persons. Stroke accounts for 15% of all deaths in patients with type 2 diabetes (14). The extent and degree of brain damage, as well as short term mortality after an ischaemic stroke is higher in diabetic patients than in non-diabetic persons, probably due to the deleterious effects of hyperglycaemia itself (15). Diabetic stroke patients more often have a history of hypertension than diabetic control patients without stroke (16), which is confirmed in the present study. A greater proportion of diabetic patients, who have recovered from stroke, will be dependent on others for daily living activities, or admitted to a nursing home for continuous care (15).

In a Dutch survey among type 2 diabetic patients of four general practitioner practices (17) evidence of cerebrovascular disease was found in 13% of the diabetic patients compared to 6% ($p=0.09$) in non-diabetic control subjects of similar age, whereas peripheral vascular abnormalities, defined as 2 non-palpable foot arteries, were found in 52% of diabetic and 21% of non-diabetic individuals ($p<0.001$). Peripheral abnormalities were more prevalent -as can be expected- in the group of patients older than 70 years. Complaints indicating coronary artery disease (Rose questionnaire) were found in 41/134 (32%) of diabetic and 26/128 (20%) of non-diabetic persons, whereas electrocardiographic signs of myocardial ischaemia (Minnesota codes 1-1, 1-2, and 7-1) were found in 18%, and 16%, respectively. Significantly more diabetic persons were treated with diuretics, beta-blocking agents and anticoagulant drugs. These prevalence data, collected in a population of diabetic patients treated by GP's, are nearly similar to the prevalence of vascular abnormalities found in the ambulatory patients treated in our hospital. Thus, the data of our ambulatory patients are representative for the population of patients with type 2 diabetes in general.

As a consequence of limitation of mobility in the nursing home patients, perhaps together with periods of poorer blood glucose control and urinary bladder dysfunction, recurrent urinary tract infections, decubitus and skin infections were seen in about 70% of them. Eight patients needed a permanent urinary bladder catheter, which again increases the predisposition for infections.

Most of the patients admitted to the nursing home will reside there permanently, only 10-20% will recover to such an extent that they can return to their homes. In the first half year after we performed our survey 2 of the 38 patients were able to leave the nursing home, whereas 7 patients died, 5 of them due to an acute cardiovascular event. Yearly costs of the stay in a nursing home average 80,000 Dutch guilders per person. An additional problem in Western

health care is the limited number of nursing home beds, and the waiting list for admission. This makes it very difficult to discharge patients from a hospital to a nursing home, placing a larger burden on the hospital staff, and in turn causing large waiting lists for hospital admission, and more often the impossibility for acute admissions.

We conclude that a cerebrovascular accident is the most frequent cause for admission of diabetic patients to a nursing home. In this group of patients peripheral vascular abnormalities, hypertension, skin necrosis or leg ulcers, and recurrent urinary tract infections were frequently encountered. Use of medication, especially diuretics and anticoagulant drugs, was high. In a group of sex-, age and diabetes therapy-matched ambulatory patients cardiac complaints were more prevalent. Blood glucose control was virtually similar in both groups, although body mass index and plasma cholesterol were higher in the ambulatory patients. Diabetes and its macrovascular complications may greatly impair the quality of life of the diabetic patient, and place a large financial and personal burden on the health care in general. Better identification of diabetic patients with high risk of stroke is necessary.

REFERENCES

1. Tattersall RB. Diabetes in the elderly - a neglected area? Diabetologia 1984; 27: 167-173.
2. Mooradian AD, Osterweil D, Petrasek D, Morley JE. Diabetes mellitus in elderly nursing home patients. A survey of clinical characteristics and management. J Am Geriatr Soc 1988; 36: 391-396.
3. Morley JE, Mooradian AD, Rosenthal MJ, Kaiser FE. Diabetes mellitus in the elderly: is it different? Am J Med 1987; 83: 533-538.
4. WHO Expert Committee on diabetes mellitus second report. World Health Organization Techn. Rep. Serv. Geneva, 1985.
5. Johnson RN, Metcalf PA, Baker JR. Fructosamine: a new approach to the estimation of serum glycosylprotein. An index of diabetic control. Clinica Chim Act 1982; 127:, 87-95.
6. Rose GA, Blackburn H, Gillum RF, Prineas RJ. Cardiovascular survey methods. 2nd ed. Geneva: World Health Organization, 1982.
7. Coodley EL. Clinical spectrum and diagnostic techniques of coronary heart disease in the elderly. J Am Geriatr Soc 1988; 36: 447-456.
8. Parmley WW. Prevalence and clinical significance of silent myocardial ischemia. Circulation 1989; 80 (suppl. IV): 68-73.
9. Jarrett RJ. Epidemiology and public health aspects of non-insulin-dependent diabetes mellitus. Epidemiol Rev 1989; 11: 151-171.
10. Levin ME, Sicard GA. Peripheral vascular disease in the person with diabetes. In: Ellenberg and Rifkin's Diabetes mellitus theory and practice, Rifkin, H., Porte Jr, D., eds, Elsevier Science Publishing Co, New York, 1990: 768-791.

11. Kreines K, Johnson E, Albrink M, *et al.* The course of peripheral vascular disease in non-insulin-dependent diabetes. Diabetes Care 1985; 8: 235-243.
12. Brand FN, Abbott RD, Kannel WB. Diabetes, intermittent claudication, and risk of cardiovascular events the Framingham study. Diabetes 1989; 38: 504-509.
13. Roccella EJ, on behalf of the Working Group on Hypertension in Diabetes. Statement on hypertension in diabetes mellitus. Arch Intern Med 1987; 147: 830-842.
14. Panzram G. Mortality and survival in type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 1987; 30: 123-131.
15. Pulsinelli WA, Levy DE, Sigsbee B, Scherer P, Plum F. Increased damage after ischemic stroke in patients with hyperglycemia with or without established diabetes mellitus. Am J Med 1983; 74: 540-544.
16. Lithner F, Asplund K, Eriksson S, Hagg E, Strand T, Wester P-O. Clinical characteristics in diabetic stroke patients. Diabete & Metabolisme 1988; 14: 15-19.
17. Verhoeven S. Treatment, follow-up and metabolic regulation of patients with diabetes mellitus type II and the prevalence of late complications in this group of patients. Thesis, Rotterdam/Heerde, 1989.

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CHAPTER 4

The value of fasting blood glucose and serum fructosamine in the evaluation of metabolic control in type 2 diabetic patients

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SUMMARY

The value of fasting blood glucose (FBG) and serum fructosamine (SF) to reliably predict glycaemic control as measured by glycosylated haemoglobin (HbA_{1c}, HPLC-method) was assessed during routine hospital visits in 264 type 2 diabetic patients on various treatments. Seventeen patients used diet only (group 1), and 126 took tablets in addition (group 2), while 89 were using insulin (group 3), and 32 insulin + sulphonylurea (group 4). Their mean age was 66 ± 11 years, known median duration of diabetes 10 (range 1-41) years, and body mass index 27.0 ± 4.2 kg/m^2; 109 patients were obese. All patients were on the same treatment for at least 2 months. HbA_{1c} and SF correlated equally well in all four patient groups ($r=0.77-0.78$, $p<0.001$). Correlation between FBG and HbA_{1c} was 0.67 for all patients ($p<0.001$). This was higher in group 1 ($r=0.75$), compared to groups 2-4 ($r=0.70$, 0.59, and 0.52, respectively). Correlation between FBG and SF was, although significant, even weaker ($r=0.44$ to $r=0.65$, $p<0.001$). In the obese patients correlation between the 3 variables was slightly better than in normal-weight patients. The within-subject correlations between the three glycaemic measures were considerably lower. In all patients a FBG <8.0 mmol/l correctly predicted HbA_{1c} below 7.5% in 64% of cases. This predictive value was 96, 66, 52 and 50% in groups 1-4. A FBG above 8.0 mmol/l was associated with a HbA_{1c} below 7.5% in 55, 16, 16, and 10% of measurements, respectively. Circadian variation of serum fructosamine, collected under standardized conditions in 15 hospitalized type 2 diabetic patients, was 6%, and of HbA_{1c} less than 2%. We conclude that in type 2 diabetic patients a normal FBG is a poor predictor of long-term adequate glycaemic control as assessed by HbA_{1c}. Serum fructosamine shows considerable variation, and has no clinical advantage over HbA_{1c} measurements.

INTRODUCTION

Many general practitioners treating patients with diabetes mellitus evaluate the degree of metabolic control by measurements of fasting or postprandial blood glucose levels, and occasionally of glycosylated haemoglobin or -as recently became more popular- serum fructosamine (SF). Fructosamine is the name for the ketoamine products of Amadori rearrangement of glycosylated plasma proteins (1-3). The quantitative determination of SF depends on the colorimetric measurement of reduction of nitroblue tetrazolium. The assay has gained its increasing popularity because of its low price and easily automated analysis. Fructosamine levels have been reported to be useful for the measurement of short-term (approximately 2 to 3 weeks) changes in blood glucose control (4,5).

A good correlation between serum fructosamine and glycosylated haemoglobin (HbA_{1c}) has been consistently found in cross-sectional investigations in both type 1 and type 2 diabetic patients (5-8). However, there remains debate how adequately normal blood glucose or fructosamine levels actually predict adequate long-term blood glucose control as assessed by HbA_{1c} determination. Agreement between both measures has been reported to be 72% or less (7-10), and within-subject variance was lower for HbA_{1c} (11). Further, factors such as travel to the hospital clinic or family physician, treatment with oral hypoglycaemic agents or insulin, and short-term changes in dietary carbohydrate intake may influence the clinical usefulness of fasting blood glucose (FBG) and SF determinations.

We assessed the relation between simultaneously and sequentially determined levels of blood glucose, serum fructosamine and glycosylated haemoglobin, and the value of FBG and SF measurements to reliably predict glycaemic control as measured by HbA_{1c} during routine hospital visits in type 2 diabetic patients on various treatments. Further, the circadian fluctuations of serum fructosamine and HbA_{1c} were studied in hospitalized patients.

MATERIALS AND METHODS

Patients

Only type 2 diabetic patients, attending the outpatient-clinic of the Department of Internal Medicine of the University Hospital Maastricht, were studied. No patient had severe kidney function abnormalities (serum creatinine above 140 µmol/l or creatinine clearance below 40 ml/min) or liver enzyme elevations. No patient was treated with corticosteroids.

Protocol 1: cross-sectional study

From 264 patients (see table 1) blood was obtained at repeated -at least two- occasions by venipuncture after an overnight fast and before taking insulin or oral hypoglycaemic agents, for determination of fasting blood glucose, serum fructosamine and HbA_{1c}. A total of 971 determinations were evaluated. Seventeen patients used diet only (group 1), 126 took oral agents in addition (group 2), while 121 were treated with insulin alone (group 3, n=89) or in combination with sulphonylurea (group 4, n=32) for at least six months.

Protocol 2: sequential study

During an 18 months period, 105 patients (age 66±10 years, body mass index, BMI 27.6±4.5 kg/m^2, median time since diagnosis of diabetes 10 (range 1-40) years, 41 males and 64 females) were followed prospectively. Blood was obtained by venipuncture during each visit to the outpatient clinic, at intervals of 1 to 4 months, for determination of fasting blood glucose, serum fructosamine and HbA_{1c}. At least five determinations were made during this period. Seven patients used diet only, 70 took oral agents in addition, while 28 were treated with insulin alone (n=17) or in combination with sulphonylurea (n=11). Type of treatment was not altered during this period, although dose adjustments were made.

Table 1. Demographic variables of the 264 patients with type 2 diabetes.

	All (n=264)	Group 1 (n=17)	Group 2 (n=126)	Group 3 (n=89)	Group 4 (n=32)
Males/females	106/158	7/10	54/72	31/58	14/18
Age (years)	66 ± 11	66 ± 12	64 ± 11	69 ± 10	67 ± 10
Body mass index (kg/m^2)	27.0 ± 4.2	27.2 ± 5.8	27.0 ± 4.2	26.7 ± 3.6	27.8 ± 5.1
Duration of diabetes (years)	10 (1-41)	2 (1-16)	8 (1-40)	14 (1-41)	10 (3-28)
Duration of insulin therapy (years)				2 (1-22)	1 (1-7)

Data as mean ± SD, or median (range)

Protocol 3: profiles

In 15 hospitalized patients (age 63 ± 13 years, BMI 29.7 ± 6.8 kg/m^2, time since diagnosis of diabetes 5 (range 1-28) years, 3 males, 12 females) five determinations of blood glucose, serum fructosamine and HbA_{1c} were made during one day. Ten patients used oral agents, 5 were on insulin. Blood was taken through an indwelling catheter at 8.00 in the fasting state, and at 11.00, 15.00, 19.00 and 23.00 hours, after 30 min rest in the supine position.

Analytical procedures

Blood glucose was measured in venous whole blood with an automated hexokinase method. Serum fructosamine was determined according to Johnson (1) after alkalinising and reduction with nitroblue tetrazolium (Sigma) on the Cobas Bio analyser. Calibration was performed with 1-desoxy-1-morphilinofructose (DMF, Sigma) in an albumin solution. The reference values of this assay are lower than those of the widely-used Fructosamine Roche kit, due to the use of a different standard and reductor. The same standards were in use during the last three years. Comparison with the Roche kit was excellent ($r=0.98$; $y=1.16x+2$, $p<0.001$). Between-assay coefficient of variation of our fructosamine determination is 4%. HbA_{1c} was determined with high pressure liquid chromatography (DIAMAT, Bio-Rad Laboratories, Richmond, Ca., USA). Normal values are 4.4-6.2%, between-assay cv is 2.6%.

Calculations and statistical analyses

Results are expressed as mean ± SD, or median and range when data were not normally distributed. Calculations were performed with the SPSS/PC+ version 3.1 statistical software package (SPSS Inc, Chicago, IL, USA). Fasting blood glucose, serum fructosamine and HbA_{1c} measurements were compared between and within subjects by Pearson's correlation coefficient based on least-squares regression analysis. Between-subject correlation was estimated as the correlation coefficient between the observations of all glycaemic variables for each patient pooled across all patients. Within-subject correlation was estimated by calculating the correlation coefficient between the observations of blood glucose, serum fructosamine and HbA_{1c} for each patient. The agreement between the measures of blood glucose control was assessed using two control categories to represent acceptable or poor control. Acceptable control was defined as fasting blood glucose below 8.0 mmol/l, and HbA_{1c} below 7.5% (4 SD above mean normal value) (12). The prognostic power of fasting blood glucose and

serum fructosamine to predict the presence of an acceptable HbA_{1c} value was calculated. The different treatment groups were compared with one-way analysis of variance, with Student-Newman-Keuls correction for multiple comparisons. P values < 0.05 were considered statistically significant.

RESULTS

Results of protocol 1

Table 1 shows the relevant demographic variables of the patient cohort studied in protocol 1. Sixty percent of patients were females. Average age was 66 years, with a range of 28 to 84 years. Figures 1A to 1C depict the distribution of fasting blood glucose, serum fructosamine and HbA_{1c} among the patients studied. A HbA_{1c} level below 7.5% was found in 23.9% of patients, and fasting blood glucose below 8.0 mmol/l was present in 38.1%. HbA_{1c} and serum fructosamine (figure 2C) proved to correlate equally well in all four patient groups, with r-coefficient varying from 0.77 (groups 1, 3 and 4) to 0.78 (group 2, all $p<0.001$). Correlation between fasting blood glucose levels and HbA_{1c} was 0.67 for all patients ($p<0.001$, figure 2B). This correlation was the highest in group 1 ($r=0.75$), and lower in the groups 2-4 ($r=0.70$, 0.59, and 0.52, respectively). Correlation between fasting blood glucose levels and serum fructosamine (figure 2A) was, although significant, even weaker ($r=0.44$ to $r=0.65$, $p<0.001$). In the obese patients, defined as body mass index above 27.0 kg/m^2 correlation between the 3 variables was slightly better than in normal-weight patients, as shown in table 2.

In all patients a fasting blood glucose <8.0 mmol/l correctly predicted a HbA_{1c} level lower than 7.5% in 64% of determinations (table 3). This predictive value was 96, 66, 52 and 50% in groups 1-4. A fasting blood glucose above 8.0 mmol/l was associated with a HbA_{1c} above 7.5% in 45, 84, 84, and 90% of measurements, respectively. Table 4 lists the sensitivity, specificity and positive and negative predictive values of fasting blood glucose level to correctly predict HbA_{1c}.

Results of protocol 2

Within-subject correlation coefficients between the measures of glycaemic control, calculated from at least five consecutive measurements, showed a wide scatter. Correlation between fasting blood glucose and both other measures was rather weak. Intra-individual correlation between serum fructosamine and

Table 2. Between-subject correlation coefficients for the three measures of blood glucose control in the different patient groups.

	FBG *vs.* SF		FBG *vs.* HbA_{1c}		SF *vs.* HbA_{1c}	
	non-obese	obese	non-obese	obese	non-obese	obese
All patients	0.58	0.63	0.64	0.70	0.76	0.82
Group 1	0.71	0.65	0.75	0.74	0.86	0.84
Group 2	0.66	0.65	0.69	0.72	0.74	0.82
Group 3	0.45	0.60	0.51	0.70	0.75	0.78
Group 4	0.46	0.48	0.59	0.49	0.74	0.81

Significance for all r-values: $p<0.001$

HbA_{1c} showed a variation from r=-0.85 to r=0.99, but mean correlation was 0.62 ($p<0.05$). No differences of within-subject correlation was found between the four treatment groups.

Results of protocol 3

Figure 3 shows the circadian changes of mean blood glucose (3A), serum fructosamine (3B) and glycosylated haemoglobin (3C). Serum fructosamine showed a significant ($p<0.05$) increase after breakfast (at 11.00 am). Intra-individual coefficient of variation (CV) of the 5 measurements of serum fructosamine varied from 1.0 to 11.0% (median 6%), and of glycosylated haemoglobin from 0.5 to 4.1% (median 1.3%, $p<0.05$ compared to CV of serum fructosamine). Overall CV of SF and HbA_{1c} were 6.3% and 2.2%, respectively. Correction of serum fructosamine for plasma total protein or albumin did not affect variation coefficient. Intra-individual CV of total protein was 4.5% (0.8-10.9%), and of albumin 5.4% (range 2.7-12.3%), and overall CV values were 5.1% and 6.1%, respectively.

DISCUSSION

In our type 2 diabetic patients the correlation between serum fructosamine and glycosylated haemoglobin was equally high irrespective of a patient's treatment. Correlation between fasting blood glucose and HbA_{1c} was the highest in

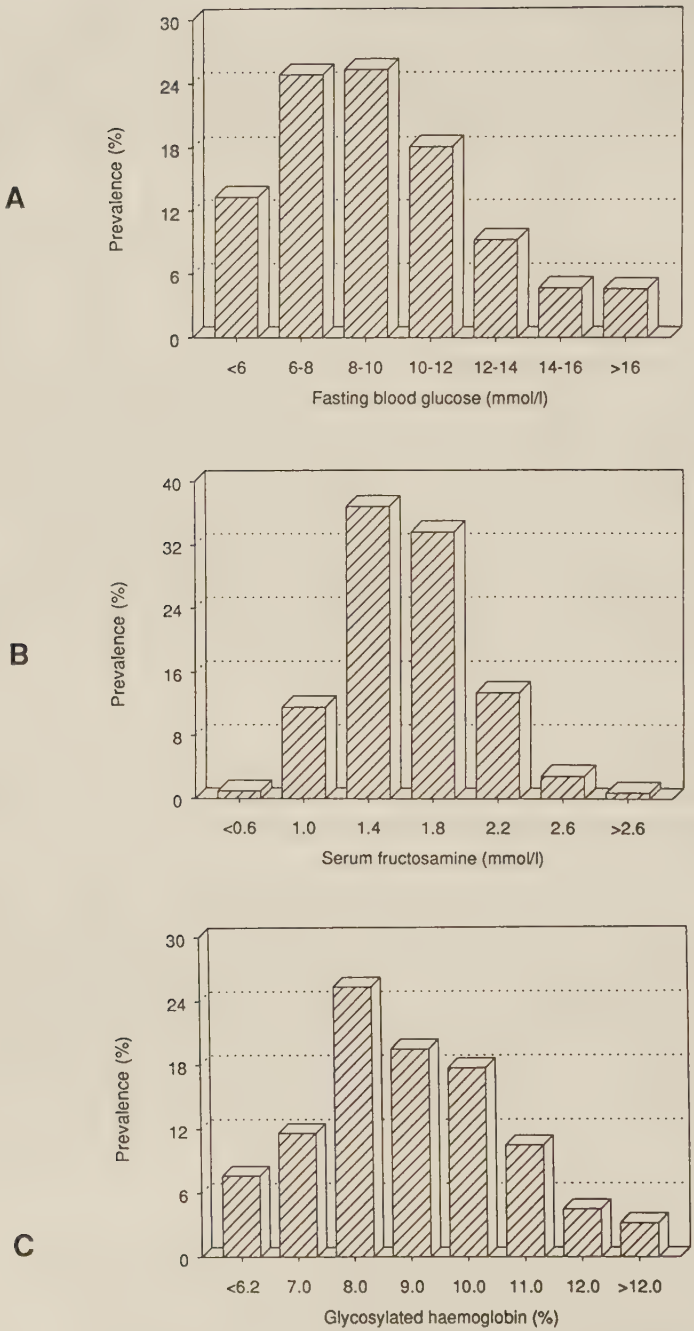

Figure 1. Distribution of fasting blood glucose (A), serum fructosamine (B) and glycosylated haemoglobin (C) among the patients studied.

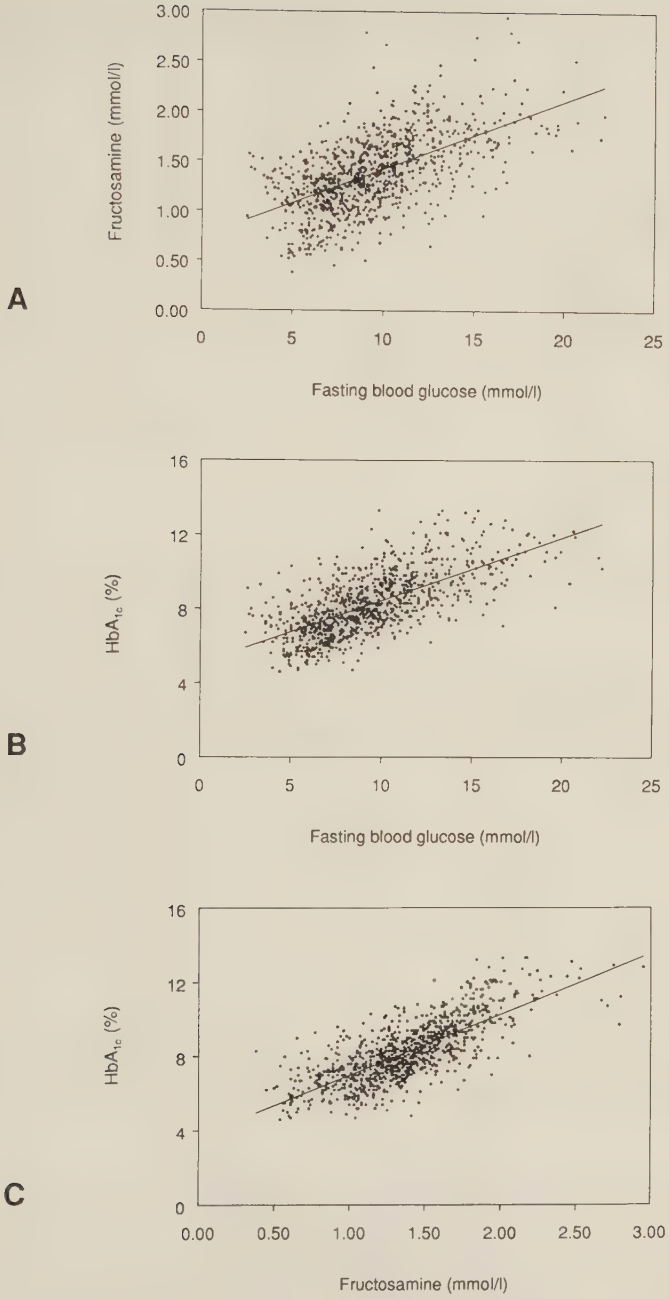

Figure 2. Relation between the three measures of blood glucose control in 264 patients followed during one year. Each point represents one individual time point for a patient. Correlations were as follows: (A) fasting blood glucose *vs.* fructosamine: r=0.59; (B) fasting blood glucose *vs.* HbA_{1c}: r=0.67; (C) HbA_{1c} *vs.* fructosamine: r=0.78; all correlations $p<0.001$.

Table 3. Cross-tabulation of levels of fasting blood glucose and glycosylated haemoglobin in the four different treatment groups (separate determinations).

			HbA_{1c} (%)	
			>7.5	< 7.5
Group 1	FBG	>8.0	5	6
	(mmol/l)	<8.0	2	47
Group 2	FBG	>8.0	319	60
	(mmol/l)	<8.0	70	135
Group 3	FBG	>8.0	108	20
	(mmol/l)	<8.0	34	37
Group 4	FBG	>8.0	76	8
	(mmol/l)	<8.0	22	22

Table 4. Diagnostic criteria evaluating the value of fasting blood glucose levels to adequately predict glycosylated haemoglobin levels in the different treatment groups.

	Sensitivity	Specificity	Pos.pred value.	Neg.pred. value
All patients	80	72	84	65
Group 1	71	89	45	96
Group 2	82	69	84	66
Group 3	76	65	84	52
Group 4	78	73	90	50

Pos.pred.value: the power of a FBG-level >8.0 mmol/l to correctly predict HbA_{1c} > 7.5%
Neg.pred.value: the power of a FBG-level <8.0 mmol/l to correctly predict HbA_{1c} < 7.5%

diet-treated patients, and significantly lower in insulin-treated patients. In all patient groups, correlation between fasting blood glucose and serum fructosamine was lower. In cross-sectional studies a significant correlation was demonstrated between serum fructosamine and glycosylated haemoglobin, with correlation coefficients varying from r=0.47 to r=0.80 (3,5-9,12). The present study confirms these results.

Table 5. Within-subject correlation coefficients for fasting blood glucose, serum fuctosamine and glycosylated haemoglobin in 105 type 2 diabetic patients.

	n	FBG *vs.* SF	FBG *vs.* HbA_{1c}	SF *vs.* HbA_{1c}
All patients	105	0.40 (0.29-0.51)	0.45 (0.36-0.54)	0.62 (0.57-0.67)[&]
Group 1	7	-0.06 (-0.56-0.45)	0.16 (-0.35-0.66)	0.70 (0.49-0.91)[&]
Group 2	70	0.47 (0.38-0.57)	0.51 (0.42-0.60)	0.62 (0.55-0.70)
Group 3	17	0.37 (0.07-0.66)	0.42 (0.14-0.70)	0.64 (0.56-0.72)[&]
Group 4	11	0.33 (-0.04-0.70)	0.35 (0.05-0.64)	0.55 (0.38-0.72)

Data as mean (95% CI);
[&] $p<0.001$ *vs.* other two correlations

A better way to describe the relation between the different glycaemic measures is to determine the correlation based on several measurements within the same individual. These within-subject correlations were much lower compared to the correlations for the entire patient group (table 2 *vs.* 5). For instance, analysis of the correlation between fructosamine and HbA_{1c} comprises both patients with a significant positive correlation, patients with no correlation, and patients with a significant negative correlation.

Although calculation of correlation coefficients readily yields significant results when a large number of patients is studied, in daily practice it is more useful to assess the power of a measure to discriminate between good and poor glycaemic control (i.e. HbA_{1c} below or above 7.5%). In our hands a fasting blood glucose level above 8.0 mmol/l correctly predicted HbA_{1c} levels exceeding 7.5%, and thus inadequate control, in the majority (84%) of our patients. However, normal blood glucose levels (below 8.0 mmol/l) predicted good control in only 65% of patients. The best predictive power was observed in diet-treated patients. In 50% of determinations in insulin-treated patients a fasting blood glucose level below 8.0 mmol/l was accompanied by a HbA_{1c} above 7.5%. This situation is unacceptable in clinical situations, and implies that determination of fasting blood glucose only may lead to false conclusions concerning long-term blood glucose control in type 2 diabetic subjects.

Serum fructosamine is regarded as a potential alternative or even a replacement of HbA_{1c} for routine clinical use in both type 1 and type 2 diabetic patients (14,15). The fructosamine assay, in use in our laboratory, is an adaptation of the Fructosamine Roche kit, with a different albumin standard. This standard was the same throughout the last 3 years, whereas the commercially available kit

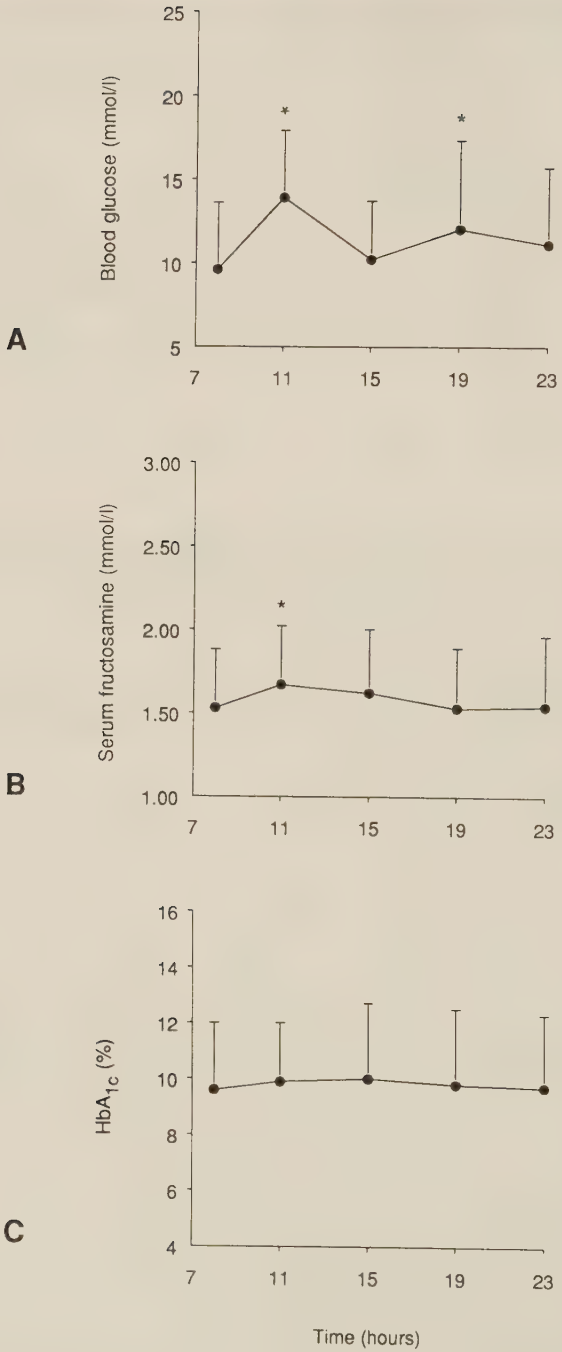

Figure 3. Circadian course of blood glucose (A), serum fructosamine (B) and glycosylated haemoglobin (C) in 15 hospitalized type 2 diabetic patients.

Table 6. Causes of discrepancy between fasting blood glucose and glycosylated haemoglobin determinations.

1. Short-term improvement or worsening of metabolic control,
   either by the diabetic state itself,
   or by non-compliance, or short-term compliance with diet or drugs
2. Insufficient postprandial insulin release,
   leading to exaggerated postprandial hyperglycaemia
3. Errors in HbA_{1c} measurement, depending on method (23):
   - abnormal haemoglobin variants (HbF, HbS)
   - haemolytic anaemia
   - renal failure
   - hyperlipoproteinaemia
   - sample storage conditions
4. Errors in blood glucose measurements:
   - reflectance meters

suffered from inacceptable variation of the standards. The modification, however, yielded different reference values for the healthy and diabetic population. The variation of serum fructosamine can be large. Changes in serum albumin may affect fructosamine concentration sufficiently to invalidate its use as a stable index of glycaemic control (16-18). Within-subject CV was estimated to be 11%, whereas between-subject variation may reach 20% (9,11). Orthostasis and venous congestion may considerably further increase variation, one study reporting a 10% increase of serum fructosamine after 10 min. walking (19). Although some authors suggest that blood samples need not be obtained in the fasting state (13,15), a circadian rhythm of SF was reported, with a significant postprandial increase, lowest values at 6 a.m. and highest values at 6 p.m. (10). Especially the latter finding prompts for standardized blood collection. Therefore, our circadian measurements were made in blood samples, collected through an indwelling catheter, with the patient in rest in the supine position for 30 min. Despite this standardized blood collection circadian variation of serum fructosamine ranged from 1 to 11%, which is significantly higher than the observed variation of HbA_{1c}, as measured by an automated HPLC-method. In addition, the postprandial increase of SF levels (10) was confirmed in our material. Others have also concluded that HbA_{1c} is a more appropriate index of blood glucose control for patients attending outpatient-clinics, considering the analytical deficiencies of serum fructosamine assays (9,11). The low price for

serum fructosamine determinations has been brought forward to promote its more extensive use in clinical medicine (13,15). Indeed, the costs of HbA_{1c} determinations (materials and personnel) with the automated HPLC-method are somewhat higher (4.10 *vs.* 2.40 Dutch guilders, table 7). Despite this difference, the fructosamine assay appears not to be the method of choice to assess glycaemic control in (elderly) diabetic patients (9), but it may complement the use of glycosylated haemoglobin.

The discussion which measurements are to be used in the evaluation of patients with type 2 diabetes in general practice has revived with the introduction of the European Consensus statement (12), and a Dutch Standard of Care (20), especially designed for use by the general practitioner (GP). Measurement of HbA_{1c} in addition to regular blood glucose determinations is generally recommended every 2 to 4 months (12). Some authors, however, state that the GP's are by far capable of assessing patient compliance, and that HbA_{1c} determinations are not needed for the routine care of patients in general practice (20). This attitude not only falsely assumes that non-compliance of patients with the diabetic regimen is readily recognized, but also disregards other factors that may limit the sole use of blood glucose measurements (table 6). Larsen and Horder (21) observed that two-thirds of patients, who were followed by their GP, had HbA_{1c} values above the acceptable level, despite random postprandial blood glucose levels, measured with reflectance meters, below 10 mmol/l. In an earlier survey we found that 15% of tablet-treated patients had fasting hyperglycaemia above 10 mmol/l, yet exhibited daytime glucose levels similar to or lower than the fasting level, leading to only slightly elevated HbA_{1c} levels. On the reverse, a considerable number of patients may show (near)-normal fasting blood glucose, but postprandial glucose increases exceeding 15.0 mmol/l. As-

Table 7. Costs of one determination of serum fructosamine and HbA_{1c}.

	Serum fructosamine	HbA_{1c} by HPLC
Chemicals	dfl. 0.90	dfl. 3.90
Costs of manpower	dfl. 1.50	dfl. 0.20
Equipment costs[#]	dfl. 0.40	dfl. 1.80

[#] serum fructosamine is determined on Cobas Bio analyser or comparable equipment, which is usually available in a laboratory setting; for HbA_{1c} the HPLC-system (DIAMAT, BioRad) has to be purchased.

suming that the latter combination means non-compliance of the patient may lead to incorrect therapeutic advices. Especially in insulin-treated patients determination of blood glucose levels both in the fasting and in the postprandial state, and of HbA_{1c} in addition (22), are necessary to adequately assess blood glucose control, and adjust insulin treatment. In all cases of discrepancy between FBG and HbA_{1c} its cause must be ascertained. Self-monitoring of blood glucose by the patient may be very helpful in this respect.

REFERENCES

1. Johnson RN, Metcalf PA, Baker JR. Fructosamine: a new approach to the estimation of serum glycosylprotein. An index of diabetic control. Clin Chim Acta 1982; 127: 87-95.
2. Armbuster DA. Fructosamine: structure, analysis and clinical usefulness. Clin Chem 1987; 33: 2153-2163.
3. Koskinen P, Irjala K, Viikari J, *et al.* Serum fructosamine in the assessment of glycaemic control in diabetes mellitus. Scand J Clin Lab Invest 1987; 47: 285-292.
4. Ashby JP, Frier BM. Is serum fructosamine a clinically useful test? Diabetic Med 1988; 5: 118-121.
5. Lapolla A, Poli T, Barison A, Fedele D. Fructosamine assay: an index of medium-term metabolic control parameters in diabetic disease. Diab Res Clin Pract 1988; 4: 231-235.
6. Cefalu WT, Mejia E, Puente GR, Fleishhacker D, Macaulay K. Correlation of serum fructosamine activity in type I diabetic children. Am J Med Sci 1989; 297: 244-246.
7. Smart LM, Howie AF, Young RJ, Walker SW, Clarke BF, Smith AF. Comparison of fructosamine with glycosylated hemoglobin and plasma proteins as measures of glycemic control. Diabetes Care 1988; 11: 433-436.
8. Mercelina LFE, Degenaar CP, Nieuwenhuijzen Kruseman AC. Bepaling van de waarden van nuchter bloedglucose en het serum fructosamine voor beoordeling van de gluco seregulering bij patiënten met niet van insuline afhankelijke diabetes mellitus. Ned Tijdschr Geneeskd 1989; 133: 1887-1890.
9. Winocour PH, Bhatnagar D, Kalsi P, Hillier VF, Anderson DC. An analysis of glycosylated blood proteins and blood glucose profiles over one year in patients with type 1 diabetes. Diabetic Med 1989; 6: 709-716.
10. Hay U, Sedlmayer A, Müller MM, Dorda W, Schernthaner G. Kritische Evaluation von Fructosamin als Kontrollparameter in der Beurteilung der diabetischen Stoffwechseleinstellung. Klin Wochenschr 1989; 67: 379-385.
11. Howey JEA, Bennet WM, Browning MCK, Jung RT, Fraser CG. Clinical utility of assays of glycosylated heamoglobin and serum fructosamine compared: use of data on biological variation. Diabetic Med 1989; 6: 793-796.
12. Alberti KGMM, Gries FA. Management of non-insulin-dependent diabetes mellitus in Europe: a consensus view. Diabetic Med 1988; 5: 275-281.
13. Negoro H, Morley JE, Rosenthal MJ. Utility of serum fructosamine as a measure of glycemia in young and old diabetic and non-diabetic subjects. Am J Med 1988; 85: 360-364.

14. Cefalu WT, Prather KL, Murphy WA, Parker TB. Clinical evaluation of serum fructosamine in monitoring elderly outpatient diabetics. J Am Geriatrics Soc 1989; 37: 833-837.
15. Morley JE. Fructosamine or glycated hemoglobin? J Am Geriatrics Soc 1989; 37: 911-912.
16. McCance DR, Coulter D, Smye M, Kennedy L. Effect of fluctuations in albumin on serum fructosamine assay. Diabetic Med 1987; 4: 434-436.
17. Dominiczak MH, Orrell JM, Finlay WEI. The effect of hypoalbuminaemia, hyperbilirubinaemia and renal failure on serum fructosamine concentration in non-diabetic individuals. Clin Chim Acta 1989; 182: 123-130.
18. Flückiger R, Woodthianed T, Berger W. Evaluation of the fructosamine test for the measurement of plasma protein glycation. Diabetologia 1987; 30: 648-652.
19. Jarausch J, Akpan W, Von Mollendorf E, Wittenbrink-Dix A, Mittmann D, Raab D. Impact of orthostasis on fructosamine values. Wiener Klin Wochenschr 1990; 102 (suppl. 180): 39-41.
20. Nederlands Huisartsen Genootschap. Standaard Diabetes Mellitus type II. Huisarts & Wetenschap 1989; 32: 7-13.
21. Larsen ML, Horder M. Metabolic evaluation of non-insulin-dependent diabetes in primary health care - the clinical usefulness of glycated haemoglobin measurements. Scand J Prim Health Care 1989; 7: 167-171.
22. Pecoraro RE, Koepsell TD, Chen MS, Lipsky BA, Belcher DW, Inui TS. Comparative clinical reliability of fasting plasma glucose and glycosylated hemoglobin in non-insulin-dependent diabetes mellitus. Diabetes Care 1986; 9: 370-375.
23. Goldstein DE, Little RR, Wiedmeyer HM, Eryland JD, McKenzie EM. Glycated hemoglobin; methodologies and clinical applications. Clin Chem 1986; 32: B64-B70.

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CHAPTER 5

Limitations of diet therapy in patients with non-insulin-dependent (type 2) diabetes mellitus

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SUMMARY

Sixty-one patients with type 2 diabetes mellitus and fasting blood glucose of 12.0 ± 0.6 mmol/l were studied before and after intensified dietary treatment in an outpatient setting. At the start of the study 33 patients were obese (body mass index >27.0 kg/m^2). Twenty patients had newly-diagnosed diabetes, median known duration of diabetes in the others was 5 years. Islet B-cell function was measured by the release of C-peptide after i.v. injection of 1 mg glucagon (area under the curve of C-peptide = C-peptide AUC), as well as calculated according to the formulae of Matthews. Insulin action was determined by measurement of fasting blood glucose and free fatty acids (NEFA) concentrations. Non-obese patients showed more severe beta-cell deficiency than the obese ones (C-peptide AUC 2586 ± 158 *vs.* 3294 ± 277 pmol/l.15min), and did not improve in metabolic control during treatment. In the obese patients three response patterns to treatment were observed: weight loss and improvement in metabolic control accompanied primarily with increased beta-cell function or increased insulin action, or worsening of metabolic control. Those with less impaired beta-cell function and shorter known duration of diabetes showed the most favourable response. In conclusion: 1) non-obese type 2 diabetic patients with fasting glucose levels above 10 mmol/l do not improve on dietary treatment alone. 2) in obese patients weight reduction is essential and results in metabolic improvement, irrespective of the preceeding fasting blood glucose concentrations. Improved beta-cell function as well as increased insulin action are responsible for this improvement.

INTRODUCTION

Non-insulin-dependent (type 2) diabetes mellitus is a heterogeneous disorder, characterized by excessive hepatic glucose production and impaired insulin-mediated peripheral glucose utilization, as well as disturbances in the recognition of glucose and the secretion of insulin by the pancreatic B-cells (1-5). Treatment of patients with type 2 diabetes mellitus aims to relieve complaints due to the hyperglycaemic state, and to normalize intermediary metabolism and body weight (5). A proper diet is still the main mode of therapy. Dietary advice, however, varies from suggestions to avoid rapidly-absorbed simple sugars and to restrict the amount of calories in overweight patients to more rigid regimens of detailed prescribed diets. Dietary therapy leading to successful weight reduction in obese patients results in an improvement of glucose metabolism (6-9). This is characterized by a reduction of hepatic glucose output (10,11) and improvement of peripheral insulin sensitivity (11). The reports on changes of the secretory response of insulin to various stimuli have been contradictory. Appropriate weight reduction, however, is not achieved easily without hospitalization of the patient and the use of aggressive dietary interventions, including supplemented fasting with a very low caloric regimen. The long-term results of dietary treatment in non-obese patients with type 2 diabetes are disappointing (12,13).

In the current study we investigated the effects of dietary management on glucose metabolism and beta-cell function in obese and non-obese patients with type 2 diabetes under circumstances more comparable with everyday practice.

MATERIALS AND METHODS

Study design

Sixty-one patients with type 2 diabetes mellitus according to the WHO criteria (12), who gave informed consent, entered the study. Patients with impaired kidney function (serum creatinine level > 120 μmol/l), severe hypertension (diastolic blood pressure >110 mm Hg and/or systolic blood pressure >200 mm Hg), liver dysfunction (transaminases and/or γGT more than two times the upper limits of normal), alcoholism or therapy with corticosteroids were excluded.

A full history and physical examination of each patient was obtained at the first visit. Patients with a body mass index (BMI) higher than 27.0 kg/m^2 were considered obese. Therapy with oral hypoglycaemic agents and other medica-

tion that might have an effect on carbohydrate-metabolism, if instituted before entering the study, was not changed during the study period. Besides routine laboratory investigations, which included the measurement of fasting blood glucose and fasting plasma insulin on two consecutive days, blood was drawn for the determination of glycosylated haemoglobin (HbA_1) and free fatty acids (NEFA). After an overnight fast, insulin secretion was studied by determining C-peptide levels after the intravenous injection of 1 mg glucagon (15). Blood was drawn before, and 5, 10 and 15 minutes after the injection of glucagon.

Thereafter, patients were carefully instructed about dietary measures by a dietician and individual diet prescriptions were given depending on a patient's physical activity and body weight. Mono- and disaccharides were excluded from the diet. Non-obese patients were prescribed a weight-maintaining diet, containing 55% carbohydrate, 30% fat and 15% protein, divided into 3 meals and 3 snacks. Energy content varied from 4788 to 10560 kJ (1140 to 2515 kcal) per day. Energy content of the diets of the obese patients was restricted, and varied from 3210 to 6175 kJ (765 to 1470 kcal) per day, with the same distribution of carbohydrate, fat and protein. In almost all patients this meant a more strict diet prescription than their preceeding food intake. To both non-obese and obese patients the importance of diet was emphasized in a comparable manner, by the dietician as well as the treating physician. Further, regular physical exercise was encouraged. Therapeutic goals were fasting blood glucose levels below 7.0 mmol/l and a body mass index below 27.0 kg/m^2.

All patients were seen monthly by the same physician and by a dietician in the outpatient-clinic. Check-ups comprised measurements of body weight, glucose profile, and HbA_1. Additional and/or more frequent check-ups were made if dictated by the condition of the patient.

In the non-obese patients, in whom no reduction of weight is desired, modifications of the diet as described might be expected to achieve effects within a number of weeks. In contrast, in the obese patients significant weight loss is desired, in which case a longer period of diet therapy is necessary. Thus, the non-obese patients were restudied (baseline measurements and glucagon-test) after 3 months, and those with overweight after six months.

For comparison glucagon-stimulated secretion of C-peptide was also measured in 18 non-obese (9 males and 9 females, age 18-48 years) and 12 obese (4 males and 8 females, age 17-49 years) control subjects.

Analytical procedures

Blood glucose concentrations were measured in venous whole blood by an automated hexokinase method. Plasma free insulin concentrations were determined by radio-immunoassay (Immuno Nuclear Corporation, USA; interassay coefficient of variation 8.5%). Plasma C-peptide levels were determined using radioimmunoassay according to Heding (16) (Novo Research Institute, Denmark, antibody M1230; interassay coefficient of variation 10%). Glycosylated haemoglobin (HbA_1) was measured by column chromatography (Bio-Rad Laboratories, Richmond, Ca., USA). Free fatty-acids were determined by a colorimetric method (17).

Calculations and statistical analyses

Beta-cell function (BCF) was assessed in two ways:

1. As the release of C-peptide after i.v. injection of 1 mg glucagon, calculated as the area under the curve (C-peptide AUC);
2. From the fasting levels of blood glucose (FBG), insulin (FIRI) and C-peptide (FCP), by calculating the following formulae (18):
   Islet B-cell function (insulin) = 20 x FIRI / 7 x (FBG - 3.5), and
   Islet B-cell function (C-peptide) = 0.286 x FCP / (FBG - 3.5),
   in which formulae insulin and C-peptide are expressed as pmol/l.

Relative insulin resistance was calculated as the proposed formula
$R = FIRI / 7 \times (22.5 \times e^{-lnFBG})$, which formula can be simplified as
$R = (FIRI \times FBG) / 7 \times 22.5$.

Data are presented as mean ± SEM, or median value when data were not normally distributed. The paired t-test was used to compare data before and after treatment, when data were normally distributed and Wilcoxon's paired test was used, when data were not normally distributed. Linear regression analysis was used to determine the relationship between two variables. P-values < 0.05 were considered to be statistically significant.

RESULTS

Parameters at entry

Of the 61 patients 33 were obese (body mass index, BMI, range 27.1-45.9, mean 31.7 ± 0.8 kg/m^2) and 28 non-obese (BMI range 18.8-27.0, mean 23.6 ± 0.4 kg/m^2). Age ranged from 24 to 80 years (median 59 years). Sixteen of the

non-obese and 14 of the obese were males. Twenty of the 61 patients were newly-diagnosed, the others had a known duration of diabetes varying from six months to twenty-two years (median 5 years). None had ever received insulin. Eight of the obese and thirteen of the non-obese patients were treated with oral hypoglycaemic agents at the start of the study.

As shown in table 1, fasting blood glucose did not differ between obese (range 6.2-26.5, mean 11.9 ± 0.8 mmol/l) and non-obese patients (range 6.6-19.7, mean 12.2 ± 0.6 mmol/l). Seven patients had fasting blood glucose levels <7.0 mmol/l (3 non-obese, 4 obese), but postprandial levels >11.0 mmol/l. Fasting levels of C-peptide were significantly higher ($p<0.05$) in the obese patients compared to the non-obese, as was the C-peptide/glucose ratio. Fasting levels of insulin were not different. The release of C-peptide after glucagon (C-peptide AUC) was significantly ($p<0.05$) higher in the obese patients. However, in both obese and non-obese patients C-peptide AUC was diminished compared to the results obtained in the control groups with corresponding body mass index. Calculated insulin resistance and islet B-cell function were similar in both patient groups, but markedly lower compared to control subjects. C-peptide AUC of both patient groups correlated with BCFcp ($r=0.57$, $p<0.01$) and with BCFiri ($r=0.46$, $p<0.01$). Serum NEFA-levels were similar in both patient groups, but markedly elevated compared to controls.

Table 1. Laboratory findings of 61 patients with type 2 diabetes before entering the study.

	Non-obese (n=28)	Obese (n=33)	Non-obese controls (n=18)	Obese controls (n=12)
Fasting blood glucose (mmol/l)	12.2 ± 0.6*	11.9 ± 0.8*	4.4 ± 0.1	4.4 ± 0.1
Glycosylated haemoglobin (%)	12.2 ± 0.4*	11.9 ± 0.5*	6.5 ± 0.1	6.7 ± 0.2
Fasting plasma insulin (pmol/l)	82 ± 10*	102 ± 11	54 ± 4	105 ± 15
Fasting plasma C-peptide (pmol/l)	529 ± 43	680 ± 56$	461 ± 33	812 ± 67
FCP/FBG (pmol/mmol)	44 ± 5*	62 ± 6*$	106 ± 7	195 ± 16
C-peptide AUC (pmol/l.15min)	2586 ± 158*	3294 ± 277*$	3853 ± 339	4965 ± 519
Islet B-cell function (insulin) (%)	39 ± 9*	44 ± 6*	207 ± 29	455 ± 113
Islet B-cell function (C-peptide) (%)	23 ± 4*	31 ± 5*	170 ± 18	311 ± 60
Relative insulin resistance	5.8 ± 0.6*	7.3 ± 1.0*	1.5 ± 0.1	2.9 ± 0.4
NEFA (mmol/l)	1.02 ± 0.10*	0.94 ± 0.09*	0.44 ± 0.03	0.47 ± 0.08

$ $p<0.05$ compared to non-obese patients; * $p<0.05$ compared to controls

Table 2. Results of dietary treatment.

	Non-obese (n=21)		Obese (n=29)	
	before	after	before	after
Body mass index (kg/m^2)	24.0 ± 0.4	24.1 ± 0.4	31.9 ± 0.8	30.3 ± 0.7*
Fasting blood glucose (mmol/l)	11.4 ± 0.6	11.9 ± 0.8	11.9 ± 0.8	10.6 ± 0.8*
Glycosylated haemoglobin (%)	11.8 ± 0.5	11.7 ± 0.5	12.1 ± 0.5	10.6 ± 0.5*
Fasting plasma insulin (pmol/l)	86 ± 11	75 ± 10	107 ± 15	87 ± 11*
Fasting plasma C-peptide (pmol/l)	523 ± 45	575 ± 57	692 ± 62	736 ± 53
FCP/FBG (pmol/mmol)	52 ± 8	55 ± 8	66 ± 8	82 ± 8*
C-peptide AUC (pmol/l.15min)	2537 ± 163	2799 ± 281	3169 ± 293	3770 ± 291*
Islet B-cell function (insulin) (%)	43 ± 11	33 ± 6	47 ± 7	54 ± 8
Islet B-cell function (C-peptide) (%)	25 ± 5	25 ± 5	31 ± 5	53 ± 11*
Relative insulin resistance	5.8 ± 0.7	5.6 ± 0.8	7.8 ± 1.1	6.0 ± 1.1*
NEFA (mmol/l)	0.95 ± 0.09	0.87 ± 0.09	1.02 ± 0.10	0.73 ± 0.06*

* $p<0.05$ compared to pre-treatment

Non-obese patients

Of the 28 non-obese patients, 7 could not be studied after three months (six had to be treated with insulin, one was lost from follow-up). Table 2 shows the changes observed in the 21 patients restudied after 3 months. Dietary management did not lead to improvement in fasting blood glucose or HbA_1 levels. Islet B-cell function did not change.

Obese patients

Of the 33 obese patients, 4 could not be studied after six months (one had to be given insulin, 3 were lost from follow-up). Thus, 29 patients were restudied after six months. As shown in table 2, BMI dropped significantly ($p<0.05$). Five patients reached a BMI below 27.0 kg/m^2. An increase in body weight was seen in 7 patients, the maximal increase was 2 kg. Seventeen of the 22 patients who lost weight showed a decrease of fasting blood glucose levels, while these levels increased in 5 of the 7 who gained weight (figure 1).

Eight patients reached fasting blood glucose within the therapeutic goal of <7.0 mmol/l. Changes of HbA_1-levels were comparable. On an average, plasma insulin levels decreased 40% in 19 of the 22 patients in whom weight reduction

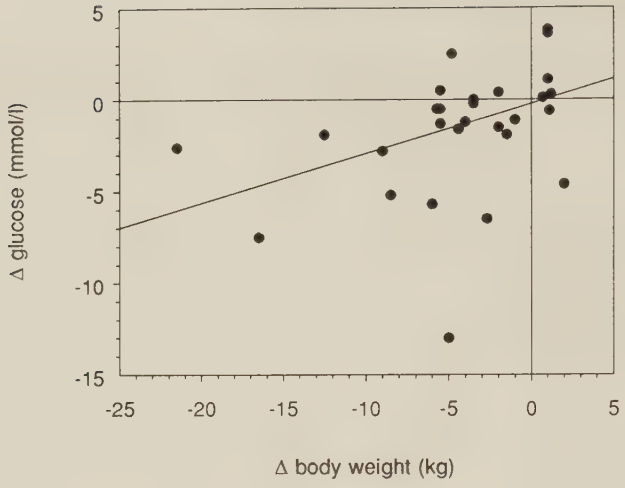

Figure 1. Relationship between the decrease in fasting blood glucose levels (mmol/l) and the decrease in body weight (kg) in 29 obese patients after six months of diet (r=0.38, p=0.04)

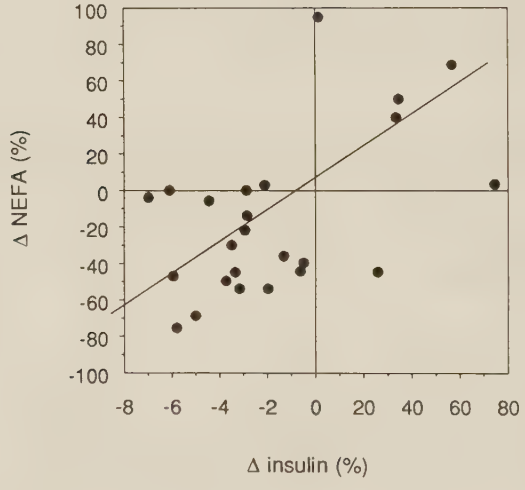

Figure 2. Relationship between the percentage change of fasting plasma insulin levels (FIRI) compared to percentage change in free fatty acid (NEFA) levels in 24 obese patients after six months' of diet (r=0.61. p=0.002).

was achieved, and increased 28% in 5 of the 7 patients who gained weight. The decrease of NEFA-levels correlated significantly with the decrease of body weight ($p<0.05$), and also with the decrease of insulin levels (figure 2).

The obese patients were subdivided on the basis of changes in their metabolic control and islet B-cell function (table 3). In 9 a decrease in fasting blood glucose (two repeated measurements) was observed together with a decrease in C-peptide release after glucagon; they were separately analysed as subgroup 1. In 10 others the decrease in fasting blood glucose was accompanied by an increase in C-peptide AUC (subgroup 2). Ten patients showed an increase in fasting blood glucose, in 9 of them (defined as subgroup 3) this increase occurred in the presence of an increase in C-peptide AUC. Figure 3 depicts the changes in islet B-cell function compared to the changes in fasting blood glucose in the different subgroups. In subgroup 1 the decrease in C-peptide AUC was accompanied by significant decreases in fasting C-peptide ($p<0.05$) and insulin ($p<0.05$) levels and also of NEFA-levels ($p<0.005$) (table 4). Patients of subgroup 2 had a lower median fasting blood glucose and body mass index at the start of the study. Their NEFA-levels did not decrease significantly. Their increase in C-peptide AUC was parallelled by a significant increase of calculated islet B-cell function (C-peptide). In subgroup 3 median levels of fasting blood glucose ($p<0.01$) and C-peptide ($p<0.05$) increased, whereas NEFA-levels remained unchanged. Body mass index increased in 4 out of these 9 patients, whereas in both other groups only one patient gained some weight. However, NEFA increased in all 4 patients who gained weight, but decreased in 4 of the 5 patients who lost weight. Median time since diagnosis of diabetes was different between the groups: this was less then 1 year in subgroup 1, and 3.5 and 6 years ($p<0.05$) in subgroups 2 and 3, respectively.

Table 3. Subgrouping of patients according to changes in fasting blood glucose and glucagon-stimulated C-peptide release.

Decrease in fasting blood glucose	decrease in C-peptide AUC	'subgroup 1'	(n=9)
	increase in C-peptide AUC	'subgroup 2'	(n=10)
Increase in fasting blood glucose	increase in C-peptide AUC	'subgroup 3'	(n=9)
	decrease in C-peptide AUC		(n=1)

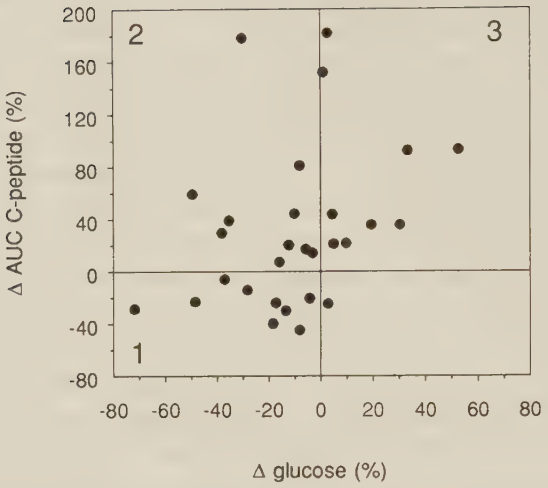

Figure 3. Relationship between the percentage change of fasting blood glucose compared to percentage change in islet B-cell function, estimated by calculating the area under the curve of C-peptide (C-peptide AUC) after intravenous injection of 1 mg. glucagon, in 29 obese patients after six months of diet. Three subgroups can be discerned:
group 1: patients in whom fasting blood glucose and C-peptide AUC decreased;
group 2: patients in whom fasting blood glucose decreased and C-peptide AUC increased;
group 3: patients in whom fasting blood glucose and C-peptide AUC increased.

DISCUSSION

In this study, intensified dietary treatment did not improve glucose or NEFA metabolism or islet B-cell function in the non-obese patients with type 2 diabetes and fasting blood glucose levels above 10 mmol/l. Previously we have shown that in a subset of these patients a slight improvement in beta-cell function could be found (19). This was however not reflected by better metabolic control. In general, the results of diet treatment in non-obese patients are disappointing: Sonksen and co-workers (12) found that only 13 out of 38 newly presenting, untreated diabetic patients within 130% of desirable body weight responded to dietary measures; the mean weight of the responders was significantly higher. Other studies (13,20) confirmed these results. Thus, it might be argued that in non-obese patients, additional therapy with oral hypoglycaemic agents or insulin should be started earlier.

In contrast, strict dietary therapy resulted in improved metabolic control in 19 of the 29 obese patients, especially in those patients who succeeded in losing weight. However, in only eight of them the therapeutic goal of fasting blood

Table 4. Results of dietary treatment in 28 obese patients.

	Subgroup 1		Subgroup 2		Subgroup 3	
	entry (n=9)	6 months	entry (n=10)	6 months	entry (n=9)	6 months
Fasting blood glucose (mmol/l)	13.4	8.3$^{\$}$	10.9	9.1$^{\#}$	11.3	14.3$^{\#}$
C-peptide AUC (pmol/l.15min)	4343	3729$^{\#}$	2540	3646$^{\$}$	2056	3968$^{\$}$
Number of patients with weight loss	8 / 9		8 / 10		5 / 9	
Body mass index (kg/m^2)	31.2	29.4$^{\#}$	28.8	27.2*	31.2	29.8
Known duration of diabetes (yrs)	< 1		3.5		6**	
Glycosylated haemoglobin (%)	11.1	9.3$^{\#}$	13.5	12.1*	12.6	11.6
Fasting plasma C-peptide (pmol/l)	1031	715*	550	573	518	747*
Fasting plasma insulin (pmol/l)	126	95*	81	60	70	66
Islet B-cell function (insulin) (%)	36	62	28	54	22	17
Islet B-cell function (C-peptide) (%)	30	48	22	29*	22	24
Relative insulin resistance	9.0	3.8*	4.6	2.7	5.5	6.5
NEFA (mmol/l)	1.22	0.59$^{\$}$	0.88	0.68	0.85	0.82

All data represent median values.
* $p<0.05$, $^{\#}$ $p<0.01$, $^{\$}$ $p<0.005$ compared to pre-treatment;
** $p<0.05$ compared to sub-group 1

glucose less than 7.0 mmol/l was reached within six months, while in only five a body mass index below the target of 27.0 kg/m^2 was reached. In general, islet B-cell function improved significantly in these patients (table 2). The decrease of free fatty acids correlated well with the decrease in body weight and fasting blood glucose. Since it has been shown previously that elevated levels of NEFA are a reflection of peripheral insulin resistance (21), the relative decrease of serum NEFA in our patients and the decreasing fasting insulin levels (figure 2) imply both a diminished resistance and enhanced insulin action.

It might be argued that a longer period of dietary treatment could have resulted in further reduction of weight and improvement of diabetic control. The proper period of dietary therapy without the prescription of additional medication still has to be established. Hadden *et al* (6) investigated the metabolic effects of intensive dietary management in 57 obese patients with type 2 diabetes. They found that after six months 42 of these patients had fasting glucose values below 8 mmol/l. Wales (7) reported more disappointing effects

of treatment of 182 patients (both obese and non-obese) with diet alone, prescribed in a normal clinical practice, without intensive education programs. Although comparisons between obese and non-obese patients are not given, a significantly greater improvement in glucose tolerance was observed in those patients who lost weight during the 3 months follow-up. Others reported good effects of very low-calorie dietary therapy (8,11). Recently, Hadden and coworkers (22) reported a prospective study concerning 223 newly-diagnosed type 2 diabetic patients. Eighty percent of them were treated by diet only for six years. The mean fasting blood glucose of these patients, which was 11.3 ± 0.3 mmol/l prior to therapy, was maintained at 8 mmol/l for two years, but rose gradually to levels of 10 mmol/l.

We studied our obese patients in 3 subgroups (table 3). The patients in subgroup 1, who showed a decrease in fasting blood glucose levels and C-peptide release, had diabetes which was recently diagnosed. In these patients there was evidence of marked insulin resistance, as assessed by high levels of free fatty acids and by a gross elevation of the calculated resistance, in the presence of moderate to severe hyperglycaemia. Further, they showed high fasting plasma C-peptide and insulin levels, and marked C-peptide release after glucagon. Dietary treatment resulted in a significant improvement in metabolic control, reflected by a 40% decrease in fasting blood glucose and almost normalization of NEFA. In subgroup 2 improvement in islet B-cell function was more prominent, whereas insulin resistance decreased only slightly. In contrast, the 9 patients in subgroup 3, who did not improve metabolic control, had a longer known duration of diabetes. Four of them actually gained weight during the treatment period. One might expect an increase in insulin resistance in these patients. Indeed, NEFA-levels increased in all 4 patients who gained weight, but decreased in 4 of the 5 patients who lost weight. Thus it seems that changes in NEFA are not only dependent on changes in fasting blood glucose, as previously described (23), but also on changes in body weight. The increase in basal and stimulated C-peptide release, that was found in these patients, was probably -at least in part- caused by the increase of fasting blood glucose levels.

Exact quantification of residual islet B-cell function remains difficult. The estimation of islet B-cell function and insulin resistance by calculation of formulae derived from a mathematical model recently has received much attention (18). In our study we compared the formulae on islet B-cell function, using fasting insulin or C-peptide concentration, with the C-peptide release measured after i.v. injection of glucagon. Both appeared to correlate well in obese and non-obese patients prior to diet therapy. However, discordant changes did occur during therapy in the obese patients, as shown in table 4. Various factors can account for the differences between calculated and measured (C-peptide AUC)

islet B-cell function. The stimulated C-peptide release may be dependent on the ambient blood glucose levels. Furthermore, it has been shown that hyperglycaemia potentiates the insulin response to other stimuli, as shown for arginine (24), to a greater degree in normal subjects than in diabetic subjects. Although the formulae of Matthews do take the ambient glucose level into account, their use should be validated in both untreated and treated diabetic patients. Changes in body weight may also be of influence on the interpretation. In addition, since there may be differences in insulin kinetics in diabetic patients compared to controls (25), the estimation of islet B-cell function using the determination of C-peptide might be preferred.

In summary, in a population of patients with type 2 diabetes mellitus defects in islet B-cell function and insensitivity to insulin were shown. Strict dietary measures did not result in improvement of metabolic control in the non-obese patients with moderate hyperglycaemia. In the obese patients three response patterns to treatment were observed: in two-thirds of patients weight loss was achieved with improvement in blood glucose control accompanied either with increased insulin action (subgroup 1) or with increased islet B-cell function (subgroup 2). In the other patients metabolic control worsened, probably due to increased insulin resistance in spite of an increased islet B-cell function. To a certain extent the pattern of response could be predicted on the basis of residual islet B-cell function and the known duration of diabetes.

REFERENCES

1. Unger RH, Grundy S. Hyperglycaemia as an inducer as well as a consequence of impaired islet cell function and insulin resistance: implications for the management of diabetes. Diabetologia 1985; 28: 119-121.
2. Efendic S, Luft R, Wajngot A. Aspects of the pathogenesis of type 2 diabetes. Endocrine Rev 1984; 5: 395-410.
3. DeFronzo RA, Ferrannini E, Koivisto V. New concepts in the pathogenesis and treatment of noninsulin-dependent diabetes mellitus. Am J Med 1983; 74 (suppl): 52-81.
4. Ward WK, Bolgiano DC, McKnight B, Halter JB, Porte Jr D. Diminished B cell secretory capacity in patients with non-insulin-dependent diabetes mellitus. J Clin Invest 1984; 74: 1318-1328.
5. Skyler JS. Non-insulin-dependent diabetes mellitus: a clinical strategy. Diabetes Care 1984; 7 (suppl. 1): 118-129.
6. Hadden DR, Montgomery DAD, Skelly RJ, *et al.* Maturity onset diabetes mellitus: response to intensive dietary management. Br Med J 1975; 2: 276-278.
7. Wales JK. Treatment of type 2 (non-insulin-dependent) diabetic patients with diet alone. Diabetologia 1982; 23: 240-245.

8. Hughes TA, Gwynne JT, Switzer BR, Herbst C, White G. Effects of caloric restriction and weight loss on glycemic control, insulin release and resistance, and atherosclerotic risk in obese patients with type II diabetes mellitus. Am J Med 1984; 77: 7-17.
9. Lipson LG, Lipson M. The therapeutic approach to the obese maturity-onset diabetic patient. Arch Intern Med 1984; 144: 135-138.
10. Bogardus C, Ravussin E, Robbins DC, Wolfe RR, Horton ES, Sims EAH. Effects of physical training and diet therapy on carbohydrate metabolism in patients with glucose intolerance and non-insulin-dependent diabetes mellitus. Diabetes 1984; 33: 311-318.
11. Henry RR, Wallace P, Olefsky JM. Effects of weight loss on mechanisms of hyperglycemia in obese non-insulin-dependent diabetes mellitus. Diabetes 1986; 35: 990-998.
12. Sonksen PH, Lowy C, Perkins JR, Lim HS. Non-insulin-dependent diabetes: 10-year outcome in relation to initial response to diet and subsequent sulfonylurea therapy. Diabetes Care 1984; 7 (suppl. 1): 59-66.
13. Taylor KG, John WG, Matthews KA, Wright AD. A prospective study of the effect of 12 months treatment on serum lipids and apolipoproteins A-I and B in type 2 (non-insulin-dependent) diabetes. Diabetologia 1982; 23: 507-510.
14. WHO Expert Committee on Diabetes Mellitus. Technical Report Series 646, 1980. Geneva: World Health Organization.
15. Poulsen S, Billesbolle P, Kolendorf K, Thorsteinsson B. The C-peptide response to glucagon injection in IDDM and NIDDM patients. Horm Metabol Res 1985; 17: 39-40.
16. Heding LG. Radioimmunological determination of human C-peptide in serum. Diabetologia 1975; 11: 541-548.
17. Laurell S, Tibbling G. Colorimetric micro-determination of free fatty acids in plasma. Clin Chim Acta 1967; 16: 57-62.
18. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and b-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-419.
19. Wolffenbuttel BHR, Weber RFA, Verschoor L. Improved insulin secretion in NIDDM by strict dietary control not accompanied by weight reduction. Diab Res Clin Pract 1985; 1: S607.
20. UK Prospective Study of therapies of maturity-onset diabetes. I. Effect of diet, sulphonylurea, insulin or biguanide therapy on fasting plasma glucose and body weight over one year. Diabetologia 1983; 24: 404-411.
21. Fraze E, Donner CC, Swislocki ALM, *et al.* Ambient plasma free fatty acid concentrations in non-insulindependent diabetes mellitus: evidence for insulin resistance. J Clin Endocrinol Metab 1985; 61: 807-811.
22. Hadden DR, Blair ALT, Wilson EA, *et al.* Natural history of diabetes presenting age 40-69 years: a prospective study of the influence of intensive dietary therapy. Quart J Med 1986; 59: 579-598.
23. Bogardus C, Lillioja S, Howard BV, Reaven GM, Mott D. Relationships between insulin secretion, insulin action, and fasting plasma glucose concentrations in nondiabetic and non-insulin-dependent diabetic subjects. J Clin Invest 1984; 74: 1238-1246.
24. Ward WK, Beard JC, Halter JB, Pfeifer MA. Porte D Jr. Pathophysiology of insulin secretion in non-insulin dependent diabetes mellitus. Diabetes Care 1984; 7: 491-502.
25. Vasquez B, Reaven GM, Andrews WJ. Elevated *in vivo* insulin clearance in Pima indians with non-insulin dependent diabetes mellitus. Diabetes 1985; 34: 671-676.

CHAPTER 6

Treatment of patients with type 2 diabetes failing on dietary therapy - Oral hypoglycaemic agents or insulin?

A randomized crossover study

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SUMMARY

In 13 non-obese patients with type 2 diabetes mellitus who failed to achieve adequate blood glucose control on dietary treatment (fasting blood glucose 13.4 ± 2.7 (± SD) mmol/l, glycosylated haemoglobin 13.0 ± 1.7%), the effects of 6 months insulin or sulphonylurea therapy on blood glucose control and lipid metabolism were compared in a randomized crossover study. Three patients, who showed a clear improvement on insulin (median glycosylated haemoglobin fell from 14.7 to 8.6%), withdrew from the study prematurely because of subjective and objective signs of hyperglycaemia after crossover from insulin to sulphonylurea. Daily dose after 6 months was 2000 mg tolbutamide (n=3), 18 ± 1 mg glibenclamide (n=7), or 34 ± 3 U insulin. On insulin, fasting (8.0 ± 1.9 mmol/l) and postprandial blood glucose (10.4 ± 2.7 mmol/l), and glycosylated haemoglobin (9.5 ± 1.1%) were lower than on sulphonylurea (11.0 ± 3.4 mmol/l, 14.4 ± 4.8 mmol/l and 11.0 ± 2.5% respectively, $p<0.05$ in each case). Median increase in body weight was greater on insulin (4.2 kg *vs.* 1.1 kg, $p<0.05$). Six patients experienced improved well-being on insulin compared with sulphonylurea. Median plasma non-esterified fatty acids decreased from 0.82 mmol/l to 0.48 mmol/l (sulphonylurea) and 0.64 mmol/l (insulin, both $p<0.05$). HDL-cholesterol was higher after insulin (1.12 ± 0.40 mmol/l) than after sulphonylurea (0.94 ± 0.25 mmol/l, $p<0.05$), and the LDL:HDL cholesterol ratio (3.27 ± 1.07 *vs.* 3.90 ± 1.08) and VLDL-triglycerides (0.67 ± 0.22 *vs.* 1.13 ± 0.40 mmol/l) were lower (both $p<0.05$). A C-peptide response after intravenous glucagon of below 5.0 nmol/l per 15min identified those patients, who had better blood glucose control with insulin.

INTRODUCTION

The treatment of patients with type 2 diabetes remains difficult. Dietary modification and regular physical exercise form the basis of treatment (1). Despite this, normoglycaemia is not achieved in a considerable number of patients. Therapy with oral hypoglycaemic agents or insulin may then be warranted. Although many patients with type 2 diabetes may have frank hyperglycaemia, specific symptoms are seldom experienced, or are not recognized as such. Thus, educating and motivating the patient for additional treatment is essential.

The comparative effects of sulphonylurea and insulin treatment on glucose metabolism and insulin action have recently come more into focus (2). Sulphonylureas stimulate the release of endogenous insulin and probably improve peripheral insulin action (3). In patients in whom intensified insulin treatment produces (near)normoglycaemia, an improvement of islet B-cell function and insulin action have been demonstrated (4,5). However, treatment with exogenous insulin might result in considerable peripheral hyperinsulinaemia (4). Furthermore, patients often hesitate to commence the uncomfortable therapy of insulin injections.

Only a few investigators have directly studied the effects of both treatment modalities in subgroups of type 2 diabetic patients failing on dietary therapy (2,6). In the current study we compared the effect of sulphonylurea treatment with that of insulin on glucose and lipid metabolism and islet B-cell function in non-obese patients with type 2 diabetes, poorly controlled on diet alone. Further, we tried to assess which parameters could predict the efficacy of either treatment in the individual patient.

PATIENTS AND METHODS

Patients

Thirteen non-obese patients (age 61 ± 3 years, body mass index, BMI 24.1 ± 0.6 kg/m^2, median time since diagnosis of diabetes 5 (range 1-22) years, 6 males) with type 2 diabetes (7) participated. The study was approved by the University Hospital ethical committee. All patients were islet-cell antibody negative, had no ketonuria, and no family history of type 1 diabetes. They were hyperglycaemic with fasting blood glucose concentrations above 8.0 mmol/l, and had a stable body weight and blood glucose control during a 3-month run-in period. In this period patients received dietary prescription depending on their physical activity. Diet contained 55% carbohydrates, with exclusion of monosaccharides

and disaccharides, 30% fat and 15% protein. Regular physical exercise was encouraged. No patient had impaired kidney function (creatinine clearance <40 ml/min), severe hypertension (diastolic blood pressure 105 mm Hg), or elevated liver enzymes, or was being treated with corticosteroids. Concomitant drug therapy was not changed during the study.

Measurements

A full history and physical examination of each patient was obtained at the first visit. Besides routine laboratory investigations, which included measurement of fasting blood glucose on 2 consecutive days, and blood glucose 2 h after breakfast and lunch (postprandial blood glucose), blood was drawn for the determination of glycosylated haemoglobin (HbA_1), non-esterified fatty acids (NEFA) and lipids. Islet B-cell function was assessed after an overnight fast by measuring fasting plasma insulin and C-peptide levels, as well as plasma C-peptide levels 5, 10, and 15 min after intravenous injection of 1 mg glucagon (8).

Study design

The effects of sulphonylurea versus insulin therapy was studied in a crossover study. Patients were randomly assigned to start with either therapy. Six patients initially started with sulphonylureas, and switched to insulin after 6 months. In the remainder the opposite regimen was followed. Insulin treatment comprised two daily injections (before breakfast and dinner) of intermediate-acting insulin (Monotard HM or Protaphane HM, Novo Industri, Bagsvaerd, Denmark), supplemented with fast-acting insulin (Actrapid HM), when postprandial blood glucose levels exceeded 11.0 mmol/l. Sulphonylurea therapy consisted of tolbutamide, given in two doses of 500-1000 mg. When adequate control could not be achieved with this drug, glibenclamide was given in two doses of 2.5-10 mg. Goals of therapy were fasting blood glucose <8.0 mmol/l, and/or HbA_1 <9.0%. Instructions on insulin injection technique and, in the majority of patients, self-monitoring of blood glucose, were given by a specialist nurse. All patients visited the outpatient-clinic 2 and 4 weeks after beginning therapy, and thereafter monthly, when measurements of body weight, glucose profile, and HbA_1 were made. For comparison, glucagontests and lipid determinations were performed in 18 non-obese (9M, 9F, aged 18-48 years) control subjects.

Analytical procedures

Blood glucose was measured in venous whole blood by an automated hexokinase method. HbA_1-concentration (normal 4.5-7.6%) was measured by column chromatography (Bio-Rad Laboratories, Richmond, CA., USA). Plasma insulin was determined by radio-immunoassay after polyethyleneglycol pretreatment (Immuno Nuclear Corporation, Stillwater, MS, USA). Plasma C-peptide levels were determined by radioimmunoassay (9) (antibody M1230, Novo Research Institute, Bagsvaerd, Denmark). Between-assay variation of insulin-RIA was 7.5%, and C-peptide 9%. NEFA were determined by a colorimetric method (10). Lipoproteins were separated by ultracentrifugation, and cholesterol and triglycerides were determined in the separate layers with enzymatic methods (Boehringer, Mannheim, FRG).

Calculations and statistical analyses

For each patient blood glucose control after 6 months insulin was compared with that after sulphonylurea by calculating the difference between the respective HbA_1-concentrations. Islet B-cell function was assessed in 3 ways:

1. As the increment of C-peptide 5 min after the iv injection of 1 mg glucagon;
2. As the incremental area under the response curve (AUC) of C-peptide, calculated by the trapezoidal rule;
3. From the fasting levels of blood glucose and insulin by calculating the degree of impairment of B-cell function (B) using the formula based on a mathematical model (11,12). Relative insulin resistance (R) was calculated with a formula based on the same model (11).

Results are expressed as mean ± SD, or median and range when data were not normally distributed. For statistical evaluations Student's paired t-test and Wilcoxon's paired test were used to compare data before and after treatment. Results in the non-diabetic subjects were compared with those of the diabetic patients using Student's unpaired t-test. The effect of period and treatment order was evaluated as described by Hills and Armitage (13). Correlations were obtained using linear regression analysis.

RESULTS

Variables at entry

Details of metabolic variables at the start of the study are given in table 1. Fasting blood glucose was 8.7 to 18.5 mmol/l (13.4 ± 2.7 mmol/l), and postprandial blood glucose 10.0 to 26.7 mmol/l (17.6 ± 4.9 mmol/l). HbA_1 was 10.3 to 15.3% (13.0 ± 1.7%). Fasting C-peptide and insulin levels were not different from control subjects, but the C-peptide:glucose ratio was greatly diminished. Islet B-cell function, estimated by the C-peptide increment 5 min after glucagon, and the release of C-peptide during the first 15 min after glucagon was greatly diminished ($p<0.001$) compared with control subjects, as was calculated islet B-cell function. Serum NEFA and total and VLDL-triglyceride levels were markedly ($p<0.001$) elevated. LDL-cholesterol (LDL-C) was higher, whereas HDL-cholesterol (HDL-C) was significantly lower ($p<0.05$) than in control subjects (table 1).

The effects of therapy

In 3 patients who received insulin initially, subjective and objective signs of hyperglycaemia occurred after they changed from insulin to sulphonylurea. This necessitated the reinstitution of insulin therapy, within 1 month after crossover in 1 patient, and after 3 months in the other 2. These 2 patients were completely evaluated at that time. Individual data of the 3 patients are shown in table 2.

Thus, complete crossover results are given for 10 patients. Daily sulphonylurea dose after 6 months was 18 ± 1 mg glibenclamide (n=7), and 2000 mg tolbutamide (n=3). Mean daily insulin dose after 6 months was 34 ± 3 (range 22-52) U. Median body weight had increased 1.1 (range -3.0 to 5.5) kg after 6 months sulphonylurea, and 4.2 (range -3.6 to 6.0 kg, $p<0.05$ compared with sulphonylurea) after insulin. During sulphonylurea, fasting blood glucose decreased to 9.8 ± 1.9 mmol/l after 2 months. Fasting blood glucose then gradually increased again to 11.0 ± 3.4 mmol/l after 6 months. With insulin therapy, fasting blood glucose decreased to 9.7 ± 2.7 mmol/l after 2 months, and to 7.4 ± 2.0 mmol/l and 8.0 ± 1.9 mmol/l after 5 and 6 months (table 3). Fasting blood glucose values were significantly lower on insulin than on sulphonylurea therapy for the whole group ($p<0.01$). HbA_1 showed comparable changes. The individual data of these variables are plotted in figure 1. Six of the 10 patients reported improved well-being, less tiredness, increased energy and a decrease

Table 1. Metabolic variables, islet B-cell function, and plasma lipids in 13 type 2 diabetic patients at start of the study, compared with 18 weight-matched control subjects.

	Diabetic patients	Control subjects
Fasting blood glucose (mmol/l)	13.4 ± 2.7 [&]	4.4 ± 0.3
Postprandial blood glucose (mmol/l)	17.6 ± 4.9 [&]	4.5 ± 0.4
Glycosylated haemoglobin (%)	13.0 ± 1.7 [&]	6.5 ± 0.5
Fasting plasma C-peptide (pmol/l)	475 (213-890)	448 (293-738)
Fasting plasma insulin (pmol/l)	46 (24-134)	50 (38-87)
C-peptide increment 5 min (pmol/l)	365 (177-593) [&]	852 (368-2265)
C-peptide AUC (nmol/l.15min)	3.7 (2.0-5.7) [&]	11.3 (4.2-26.2)
B (% islet B-cell function)	18 (8-39) [&]	152 (111-537)
R (relative insulin resistance)	4.5 (1.4-11.3) [&]	1.4 (1.0-2.3)
NEFA (mmol/l)	0.82 (0.58-2.6) [&]	0.48 (0.10-0.75)
LDL-cholesterol (mmol/l)	3.67 ± 0.84 [$]	2.76 ± 0.66
HDL-cholesterol (mmol/l)	0.93 ± 0.21 [*]	1.26 ± 0.46
LDL:HDL cholesterol ratio	4.07 ± 1.43 [&]	2.45 ± 0.91
Triglycerides (mmol/l)	2.35 ± 1.00 [$]	1.01 ± 0.35
VLDL-triglycerides (mmol/l)	0.86 (0.26-4.5) [*]	0.43 (0.18-1.32)

Mean ± SD, or median (range);
[*] $p<0.05$, [$] $p<0.005$, [&] $p<0.001$ compared to control subjects

Table 2. Blood glucose control and measures of islet B-cell function in 3 patients who withdrew from the study.

	Baseline	Insulin	Sulphonylurea[a]
Fasting blood glucose (mmol/l)	12.0-18.5	4.4-8.6	12.1-16.7
Post-prandial blood glucose (mmol/l)	18.3-28.2	10.1-15.6	19.3-26.5
Glycosylated haemoglobin (%)	13.3-15.3	8.1-10.0	11.5-12.6
Fasting plasma insulin (pmol/l)	37-93	63-102	38-63
Fasting plasma C-peptide (pmol/l)	461-837	453-695	815-958
C-peptide AUC (nmol/l.15min)	2.1-4.3	2.7-11.2	5.6-7.7

Data are presented as range.
[a] Only measured in 2 patients, 3 months after crossover from insulin to sulphonylureas

in urine production during insulin therapy compared with sulphonylurea. Severe hypoglycaemia necessitating medical assistance was not observed.

Islet B-cell function

Fasting C-peptide, the fasting C-peptide:glucose ratio, the increment of C-peptide 5 min after glucagon, and C-peptide AUC did not change significantly (table 3). Fasting plasma free insulin levels only increased during the insulin period ($p<0.05$ compared with sulphonylurea). The calculated islet B-cell function did not change during sulphonylurea therapy, neither did calculated relative insulin resistance.

Table 3. Comparison of insulin and sulphonylurea therapy in 10 non-obese patients: effects on blood glucose control, measures of islet B-cell function, and plasma lipids.

	Sulphonylurea	Insulin
Fasting blood glucose (mmol/l)	11.0 ± 3.4 *	8.0 ± 1.9 #&
	(5.6-14.9)	(5.0-11.8)
Post-prandial blood glucose (mmol/l)	14.4 ± 4.8	10.4 ± 2.7 #$
	(7.4-21.1)	(7.3-14.5)
Glycosylated haemoglobin (%)	11.0 ± 2.5 *	9.5 ± 1.1 #$
	(7.0-14.9)	(7.7-11.0)
Fasting plasma C-peptide (pmol/l)	612 (209-960)	410 (208-829)
Fasting plasma insulin (pmol/l)	63 (25-103)	72 (42-181) #$
C-peptide increment 5 min (pmol/l)	503 (241-1554)	372 (172-947)
C-peptide AUC (nmol/l per 15-min)	6.4 (2.4-18.8)	4.0 (1.3-10.6)
B (% islet B-cell function)	22 (7-107)	
R (relative insulin resistance)	3.4 (2.0-8.4)	
NEFA (mmol/l)	0.48 (0.31-1.38) *	0.64 (0.35-0.85) *
LDL-cholesterol (mmol/l)	3.57 ± 0.92	3.42 ± 0.85
HDL-cholesterol (mmol/l)	0.94 ± 0.25	1.12 ± 0.40 $
LDL:HDL cholesterol ratio	3.90 ± 1.08	3.27 ± 1.07 $
Triglycerides (mmol/l)	1.79 ± 0.45	1.51 ± 0.38
VLDL-triglycerides (mmol/l)	1.13 ± 0.40	0.67 ± 0.22 &

Mean ± SD, or median (range);
* $p<0.05$, # $p<0.01$ compared with pre-treatment;
$ $p<0.05$, & $p<0.01$ compared with sulphonylurea therapy

Plasma lipids

The effects of therapy on lipid metabolism are given in table 3. NEFA showed a marked decrease ($p<0.05$) with both treatments. Compared with baseline, the levels of LDL-cholesterol and HDL-cholesterol, as well as total triglycerides did not change. However, HDL-cholesterol was higher ($p<0.05$), and the LDL:HDL cholesterol ratio ($p<0.05$), and VLDL-triglycerides ($p<0.01$) were lower after insulin than after sulphonylurea.

Islet B-cell function and effect of therapy

Figure 2 shows the relationship between C-peptide AUC and therapy outcome, as assessed by the difference between HbA_1 after 6 months insulin and that after sulphonylurea. The data of 12 patients are presented, including the two patients who were evaluated only 3 months after switching from insulin to sulphonylurea. C-peptide AUC correlated well with this difference in HbA_1 ($r=0.70$, $p=0.012$). A low C-peptide secretory capacity, reflected by an C-peptide AUC below 5.0 nmol/l.15min identified those patients, who exhibited better blood glucose control on insulin therapy than on sulphonylurea. A similar correlation was found between the difference in HbA_1 and the increment of C-peptide 5 min after glucagon ($r=0.64$, $p=0.022$).

DISCUSSION

There are few studies which compare the effects of sulphonylurea and insulin on blood glucose control in type 2 diabetic patients who have failed on dietary therapy. Tolazamide and insulin equally improved blood glucose control in obese patients (2). In non-obese newly-diagnosed type 2 diabetic patients insulin therapy resulted in better blood glucose control and improved islet B-cell response to oral glucose to a greater extent than sulphonylureas (6). There were, however, some differences in pre-study blood glucose control: the mean fasting blood glucose was 10.0 mmol/l in the former, and 12.9 mmol/l in the latter study. In the U.K. Prospective Diabetes Study (14,15) the effects of oral hypoglycaemic agents and insulin have been reported in a large parallel study in newly-diagnosed diabetic patients, who failed to achieve normal fasting plasma glucose levels after dietary therapy. An equal effect of sulphonylurea and insulin on blood glucose control in both obese and non-obese patients was found. As a group the patients studied had comparatively moderate hyper-

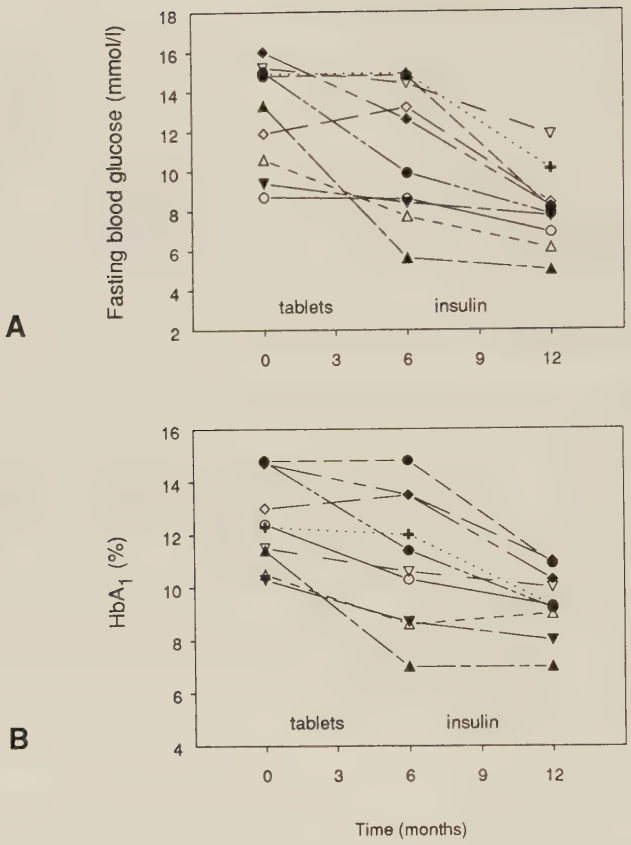

Figure 1. Course of fasting blood glucose (A) and glycosylated haemoglobin (B) during therapy with sulphonylurea ('tablets') and insulin in the 10 individual patients who completed the study.

glycaemia at the start of the treatment period (mean fasting plasma glucose 8.5 ± 1.9 mmol/l).

In our non-obese type 2 diabetic patients we found significantly better blood glucose control, as measured by fasting and postprandial blood glucose and HbA_1, on insulin than on sulphonylurea therapy, together with a clear improvement in clinical well-being. There was a moderate increase in body weight with both treatments, higher with insulin. Measures of islet B-cell function did not change, whereas fasting insulin levels did increase. HDL-cholesterol was significantly higher, and the LDL:HDL cholesterol ratio and VLDL-triglycerides were lower on insulin than on sulphonylurea therapy.

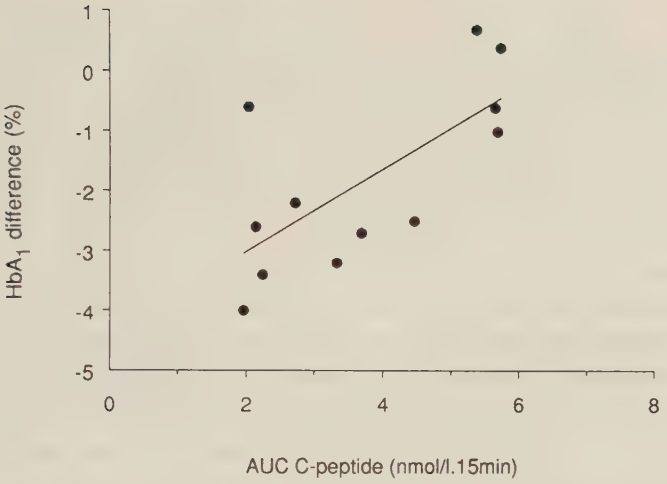

Figure 2. The relationship between the incremental C-peptide response after i.v. glucagon (C-peptide AUC) and the difference between HbA_1 after insulin and HbA_1 after sulphonylurea therapy in 12 patients with type 2 diabetes. Ten of these are patients who completed the study; 2 additional patients were evaluated after having used only 3 months sulphonylurea therapy. Linear regression yields a r-value of 0.70, p=0.012.

Despite our efforts, only in 7 of the 13 patients it was possible to achieve adequate blood glucose control (fasting blood glucose <8.0 mmol/l) on insulin, and only 2 achieved adequate control on sulphonylurea. It is known that most patients with type 2 diabetes do not report or even recognize hyperglycaemic complaints, despite the fact that they may be in rather bad control. Although our patients had reported no or only mild hyperglycaemic symptoms during dietary therapy, they experienced improved well-being as soon as blood glucose control was improved. The initial lack of symptoms of hyperglycaemia may negatively influence dietary and drug compliance.

Ten of the 13 patients had fasting blood glucose levels above 11.0 mmol/l. On clinical grounds our patients were classified as non-insulin-dependent patients in whom adequate dietary treatment failed to normalize glycaemic control. Although their fasting insulin and C-peptide levels were similar to those of control subjects matched for body weight, a lower C-peptide response after glucagon was found. Earlier studies (6,15) suggested that in such patients maximal-dose sulphonylurea therapy does not always normalize blood glucose control. Our data support this. However, in clinical practice sulphonylurea therapy would commonly be prescribed to these patients in order to achieve better control while avoiding insulin injections. Although good responders to oral hypoglycaemic agents generally have better islet B-cell function than poor

responders, some patients with low insulin secretory capacity can respond favourably to oral agents. Others with good islet B-cell function will not (16). Since we found the lowest blood glucose values in our patients after 2-3 months of sulphonylurea, the effects of this therapy in a given patient can be assessed within a few months. When blood glucose control does not normalize, insulin therapy is warranted. Nevertheless, patients with only moderate hyperglycaemia often hesitate to start insulin therapy.

Determination of residual islet B-cell function can be useful to identify patients who might benefit from insulin therapy (17,18), or to distinguish between individuals with type 1 or type 2 diabetes (19,20). Usually, only fasting and 6 min post-glucagon values of C-peptide are used. All our patients with a C-peptide release after glucagon below 5.0 nmol/l.15min exhibited better blood glucose control on insulin than on sulphonylureas. Other measures of islet B-cell function (fasting C-peptide levels, the C-peptide:glucose ratio) did not have any discriminatory power, nor did the calculated islet B-cell function. The formulae for these calculations are based on computer model predictions for the quantification of residual islet B-cell function of diet-treated diabetic patients in the basal state (11). The validity of these formulae for the interpretation of data collected in diabetic patients treated with insulin or oral hypoglycaemic agents still has to be determined. Based on our present findings we propose the use of the glucagon stimulationtest with measurement of C-peptide response over at least 15 min, both for the quantification of residual islet B-cell function, and to decide which patients with type 2 diabetes, having failed on dietary therapy, should receive insulin. The C-peptide increment after 5 min can also be used for this purpose, but this variable has a slightly less discriminatory power.

After insulin therapy the plasma HDL-cholesterol was higher and VLDL-triglycerides were lower than after sulphonylurea. There were no differences in LDL-cholesterol between treatments. Previous studies on the effects of insulin treatment and the resulting improvement in blood glucose control on HDL-cholesterol have yielded controversial results, as reviewed by Reaven (21). It is not yet known whether improvement of blood glucose control will also improve the lipid profile. In our small group of patients no correlation could be found between the improvement in HDL-cholesterol and changes in fasting blood glucose, HbA_1, insulin levels or islet B-cell function.

In conclusion, insulin therapy was superior to sulphonylurea in non-obese patients with type 2 diabetes who were markedly hyperglycaemic despite dietary therapy. By determination of C-peptide release after glucagon it was possible to identify those patients in whom insulin therapy resulted in better blood glucose control than sulphonylurea.

REFERENCES

1. Skyler JS. Non-insulin-dependent diabetes mellitus: a clinical strategy. Diabetes Care 1984; 7 (suppl. 1): 118-129.
2. Firth RG, Bell PM, Rizza RA. Effects of tolazamide and exogenous insulin on insulin action in patients with non-insulin-dependent diabetes mellitus. New Engl J Med 1986; 314: 1280-1286.
3. Gerich JE. Sulfonylureas in the treatment of diabetes mellitus. Mayo Clin Proc 1985; 60: 439-443.
4. Garvey WT, Olefsky JM, Griffin J, Hamman RF, Kolterman OG. The effect of insulin treatment on insulin secretion and insulin action in type II diabetes mellitus. Diabetes 1985; 34: 222-234.
5. Ginsberg H, Rayfield EJ. Effect of insulin therapy on insulin resistance in type II diabetic subjects-evidence for heterogeneity. Diabetes 1981; 30: 739-745.
6. Samanta A, Burden AC, Kinghorn A. A comparative study of sulphonylurea and insulin therapy in non-insulin-dependent diabetics who had failed on diet therapy. Diabetes Res 1987; 4: 183-185.
7. WHO Expert Committee on Diabetes Mellitus. Technical Report Series 727, 1985. Geneva: World Health Organization.
8. Poulsen S, Billesbolle P, Kolendorf K, Thorsteinsson B. The C-peptide response to glucagon injection in IDDM and NIDDM patients. Horm Metabol Res 1985; 17: 39-40.
9. Heding LG. Radioimmunological determination of human C-peptide in serum. Diabetologia 1975; 11: 541-548.
10. Laurell S, Tibbling G. Colorimetric micro-determination of free fatty acids in plasma. Clin Chim Acta 1967; 16: 57-62.
11. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and b-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-419.
12. Rudenski AS, Hadden DR, Atkinson AB *et al.* Natural history of pancreatic islet B-cell function in type 2 diabetes mellitus studied over six years by homeostasis model assessment. Diabetic Med 1987; 5: 36-41.
13. Hills M, Armitage P. The two-period cross-over clinical trial. Br J Clin Pharmacol 1979; 8: 7-20.
14. UK Prospective study of therapies of maturity-onset diabetes: I. Effect of diet, sulphonylurea, insulin or biguanide therapy on fasting plasma glucose and body weight over one year. Diabetologia 1983; 24: 404-411.
15. UK Prospective study of therapies of maturity-onset diabetes: II. Reduction in Hba1c with basal insulin supplement, sulfonylurea, or biguanide therapy. Diabetes 1985; 34: 793-798.
16. Lebovitz HE. Oral hypoglycemic agents. In: The Diabetes Annual/3, eds. Alberti KGMM and Krall LP. Amsterdam, Elsevier, 1987, 72-93.
17. Malmquist J, Birgerstam G. Assays of pancreatic B cell secretory products: utility in investigative and clinical diabetology. Scand J Clin Lab Invest 1986; 46: 705-713.
18. Koskinen P, Viikari J, Irjala K, Kaihola HL, Seppala P. C-peptide determination in the choice of treatment in diabetes mellitus. Scand J Clin Lab Invest 1985; 45: 589-597.

19. Katzeff HL, Savage PJ, Barclay-White B, Nagulesparan M, Bennett PH. C-peptide measurement in the differentiation of type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 1985; 28: 264-268.
20. Turner RC, Holman RR, Matthews DR, O'Rahilly SP, Rudenski AS, Braund WJ. Diabetes nomenclature: classification or grading of severity? Diabetic Med 1986; 3: 216-220.
21. Reaven GM. Abnormal lipoprotein metabolism in non-insulin-dependent diabetes mellitus. Am J Med 1987; 83 (suppl.3A): 31-40.

CHAPTER 7

Insulin therapy in type 2 diabetic patients with secondary failure to oral hypoglycaemic agents

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SUMMARY

In 26 type 2 diabetic patients with failure to diet and sulphonylureas (fasting blood glucose levels >8.0 mmol/l) the effects of insulin therapy on blood glucose control, islet B-cell function and plasma lipids were studied. Age was 58 ± 11 (SD) years, median duration of diabetes 6.5, range 1-24 years, and body mass index 24.5, range 18.9-36.3 kg/m^2. Six patients were obese. Therapy comprised twice daily injections of intermediate-acting insulin with additional fast-acting insulin when necessary. After 6 months, insulin dose was 39 ± 10 U in the non-obese patients. Their fasting (14.0 ± 2.7 mmol/l) and post-prandial blood glucose (17.9 ± 4.5 mmol/l) and glycosylated haemoglobin (HbA_1, 13.0 ± 2.0%) declined to 7.7 ± 1.6 mmol/l, 10.6 ± 2.6 mmol/l and 9.5 ± 1.0%, respectively ($p<0.001$). Median body weight increase was 3.7 kg ($p<0.001$). The changes in body weight correlated well with the changes in fasting blood glucose ($r=-0.75$, $p<0.01$) and HbA_1 ($r=-0.73$, $p<0.01$). Fasting plasma insulin levels increased ($p<0.01$), whereas fasting plasma C-peptide and C-peptide release after glucagon did not change. Free fatty acids, LDL-cholesterol, total and VLDL-triglycerides showed a significant ($p<0.05$) decrease during insulin treatment. In the 6 obese patients insulin dose after 6 months was 44 ± 18 U. Their fasting blood glucose fell from 11.3 ± 2.2 to 8.8 ± 2.7 mmol/l ($p<0.01$), and HbA_1 decreased from 10.7 ± 1.1% to 9.8 ± 1.3% ($p<0.01$). Body weight remained unchanged. Fasting C-peptide levels decreased ($p<0.01$), whereas insulin levels nor lipid parameters showed significant changes. Almost all patients reported improved well-being. One patient had a hypoglycaemic period, requiring medical assistance. We conclude that insulin therapy in type 2 diabetic patients failing on sulphonylurea therapy greatly improved metabolic control with a slight improvement of lipid profile, despite a concomitant gain of weight.

INTRODUCTION

Dietary modification and regular physical exercise form the basis of treatment of patients with type 2 diabetes (1-3). Despite this, normoglycaemia is not easily achieved in a considerable number of patients (3,4). Additional therapy with oral hypoglycaemic agents, for instance sulphonylureas, is generally recommended (5). However, the duration of clinical effectiveness of sulphonylureas is limited. The incidence of so-called secondary failure (6,7) to oral agents is about 10% per year. In patients compliant with diet, who show deterioration of blood glucose control on oral hypoglycaemic agents, temporary or permanent insulin therapy is warranted. This treatment however poses new problems, such as weight gain, and the risk of hypoglycaemias (8). Further, the occasional necessity of administering high insulin doses, especially in obese patients (9), may result in high peripheral insulin levels, which are associated with an increased risk for the development of atherosclerosis and hypertension (10). Finally, it is essential to educate and motivate patients for insulin therapy. Many patients with secondary failure may have frank hyperglycaemia and are prone to develop diabetic complications more rapidly, yet specific symptoms due to the hyperglycaemia seldomly are experienced (11).

Various insulin injection schemes have been proposed (12), such as once daily regimens of long-acting insulin on waking or retiring (13-15), or twice daily injections. In a small number of patients even multiple subcutaneous injections or CSII have been employed (7,8). In the current study we investigated the effects of conventional twice-daily insulin treatment, started at the outpatient-clinic, on blood glucose control, islet B-cell function and plasma lipids in type 2 diabetic patients with secondary failure to sulphonylurea therapy.

MATERIALS AND METHODS

Patients

Twenty-six patients with type 2 diabetes (16), who were referred by their general practitioner because of inadequate blood glucose control, entered the study. All patients were hyperglycaemic (fasting blood glucose >8.0 mmol/l), despite diet and maximal doses of glibenclamide or gliclazide. Twenty patients were non-obese, defined as body mass index (BMI) below 27.0 kg/m^2. Their age ranged from 32-76 years (60 ± 11 years), and time since diagnosis of diabetes 1-24 years (median 6 years). Ten of them were males. Six patients were

obese (BMI 31.2 ± 2.9 kg/m^2), with age 29-61 years (median 55 years), and time since diagnosis 4.5-20 years (median 7 years). All patients were islet-cell antibody negative.

During an initial 3-month run-in period patients received diet prescriptions depending on their physical activity. Mono-and disaccharides were restricted. The diet contained 55% carbohydrates, 30% fat and 15% protein. Regular physical exercise was encouraged. During this period all patients had a stable body weight and blood glucose control. No patient had impaired kidney function (creatinine clearance <40 ml/min), severe hypertension (diastolic blood pressure 105 mm Hg), elevated liver enzymes, or was being treated with corticosteroids. Concomitant therapy, such as antihypertensive treatment and diuretics, were not changed during the study period.

Measurements

A full history and physical examination of each patient was obtained at the first visit. Laboratory investigations included the measurement of fasting blood glucose on two consecutive days and of blood glucose 2 hours after breakfast and lunch (yielding average postprandial blood glucose), and the determination of glycosylated haemoglobin (HbA_1), free fatty acids (NEFA) and plasma lipids. Islet B-cell function was assessed after an overnight fast by measuring plasma C-peptide levels before, and 5, 10 and 15 min after intravenous injection of 1 mg glucagon (17). Between two and four days later patients underwent a meal test, employing the breakfast they would normally eat according to their individual diet prescription. Blood glucose and plasma insulin were determined before (in the fasting state), and 2 hours after the start of breakfast. Oral hypoglycaemic agents were taken just prior to the meal.

Study design

During the run-in period patients were instructed in insulin injection technique and–in the majority of patients–home-monitoring of blood glucose, by a specialist nurse in the outpatient clinic. Insulin treatment comprised two daily doses (before breakfast and before supper) of intermediate-acting insulin (Monotard HM or Protaphane HM, Novo Industri, Bagsvaerd, Denmark), supplemented with short-acting insulin (Actrapid HM) when postprandial blood glucose levels exceeded 11.0 mmol/l. Goals of the therapy were fasting blood glucose levels <8.0 mmol/l, and/or HbA_1 <9.0%.

All patients visited the outpatient clinic 2 and 4 weeks after beginning of insulin therapy, and thereafter monthly. Check-ups comprised measurements of body weight, glucose profile, and HbA_1. Insulin dose was adjusted according to the results of blood glucose monitoring. After 6 months insulin therapy, measurements performed at baseline were repeated. Breakfasts were identical to the meals taken before the institution of insulin therapy. Now insulin was administered, half an hour before the start of the meal.

For comparison breakfast and glucagon-tests and determinations of plasma lipids were performed in 18 non-obese (9M, 9F, age 18-48 years) and 12 obese (4M, 8F, aged 17-49 years) control subjects.

Analytical procedures

Blood glucose was measured in venous whole blood by an automated hexokinase method. HbA_1-concentration (normal values 4.5-7.6%) was measured by column chromatography (Bio-Rad Laboratories, Richmond, CA., USA). Plasma free insulin was determined by radio-immunoassay after polyethyleneglycol pretreatment (Immuno Nuclear Corporation, Stillwater, MS, USA). Plasma C-peptide levels were determined using radioimmunoassay (18) (antibody M1230, Novo Research Institute, Bagsvaerd, Denmark). Between-assay variation of insulin-RIA was 7.5%, of C-peptide 9%. Free fatty-acids (NEFA) were determined by a colorimetric method (19). Lipoproteins were separated by ultracentrifugation, and cholesterol and triglycerides were measured in the separate layers with enzymatic methods (Boehringer, Mannheim, FRG).

Calculations and statistical analyses

Islet B-cell function was assessed in three ways:

1. as the ratio of fasting plasma C-peptide and blood glucose levels;
2. by the increment of C-peptide 5 min after iv injection of 1 mg glucagon;
3. as the incremental area under the response curve (AUC) of C-peptide, calculated with the trapezoidal rule. Since it is known that the ambient blood glucose level influences the amount of C-peptide released, the ratio of C-peptide AUC and fasting blood glucose was also calculated.

Results are expressed as means ± SD, or median and range when data were not normally distributed. The Student's paired t-test and Wilcoxon's paired test were used when appropriate. Linear regression analysis was used to determine the relationship between two variables. P-values <0.05 were considered to be statistically significant.

Non-obese patients

Details of the various variables in the non-obese patients just prior to the start of insulin therapy are given in table 1-3. Fasting blood glucose was 8.4 to 18.5 mmol/l (14.0 ± 2.7 mmol/l), postprandial blood glucose was 7.4 to 28.2 mmol/l (17.9 ± 4.6 mmol/l), and HbA_1 was 8.7 to 18.1% (13.0 ± 2.1%). Median fasting C-peptide was 483 (range 132-890 pmol/l), fasting insulin levels were 8 to 134 pmol/l (median 45 pmol/l). Islet B-cell function was significantly lower ($p<0.001$) than in control subjects. NEFA, LDL-cholesterol, total plasma and VLDL-triglycerides were significantly higher compared with control subjects, and HDL-cholesterol was lower.

The effects of therapy

Metabolic control

Daily insulin dose in the 20 non-obese patients after 6 months was 39 ± 10 (range 22 to 58) U. Median body weight increase was 4.5 (range -2.0 to +10.7) kg. Two patients lost some weight, although their blood glucose control improved. The changes in fasting and postprandial blood glucose and HbA_1 are depicted in table 1.

Eleven patients achieved the desired goal of fasting blood glucose <8.0 mmol/l, while two patients still had fasting blood glucose above 10.0 mmol/l after 6 months. Eight patients achieved HbA_1 values <9.0%. Seven patients still were marked hyperglycaemic with fasting blood glucose above 8.0 mmol/l, and postprandial blood glucose above 11.0 mmol/l. These seven patients had slightly higher blood glucose just prior to the start of insulin therapy compared with the other 13 patients (fasting blood glucose: 15.5 ± 2.1 *vs.* 13.2 ± 2.8 mmol/l, $p=0.08$, and postprandial blood glucose: 20.8 ± 4.0 *vs.* 16.4 ± 4.2 mmol/l, $p=0.04$). Their age, body mass index, duration of diabetes and islet B-cell function, however, were not different. Also, their insulin dose after 6 months was similar (44 *vs.* 37 U). Figure 1 depicts the changes in fasting blood glucose in the individual patient in relation to the change in body weight. Both variables correlated significantly ($r=-0.75$, $p<0.01$), a larger decrease in fasting blood glucose implying a larger increase in body weight. A similar relation was found between change in body weight and HbA_1 ($r=-0.73$, $p<0.01$).

Table 1. Effects of twice daily insulin therapy on body weight and blood glucose control in 20 non-obese patients with type 2 diabetes failing on sulphonylurea therapy.

		insulin	
	baseline	3 months	6 months
Weight change (kg)		+2.9 #	+4.5 &#
median (range)		-2.0-+6.2	-2.0-+10.7
Fasting blood glucose (mmol/l)	14.0 ± 2.7	8.7 ± 2.1 #	7.7 ± 1.7 #
Postprandial blood glucose (mmol/l)	17.9 ± 4.6	11.0 ± 2.9 #	10.6 ± 2.6 #
Glycosylated haemoglobin (%)	13.0 ± 2.1	10.9 ± 1.4 #	9.5 ± 1.0 &#

Mean ± SD, or median (range)
& p<0.001 compared to 3 months;
# p<0.001 compared to pre-treatment

Table 2. Effects of twice daily insulin therapy on parameters of islet B-cell function in the 20 non-obese patients.

	before	insulin	controls
Fasting plasma C-peptide (pmol/l)	483	310	448
	132-890	104-829	293-738
Fasting plasma C-peptide/blood glucose	33.6 c	45.1 c	109
	8.1-74	12.7-106	63-149
Fasting plasma insulin (pmol/l)	45	66 #	50
	8-134	28-198	38-87
Post-prandial plasma insulin (pmol/l)	106	131 *b	71
	43-269	76-692	38-269
C-peptide AUC (nmol/l.15-min)	2.9 c	3.9 c	11.3
	0.4-9.0	0.9-11.2	4.1-26.2
C-peptide AUC/fasting blood glucose	0.2 c	0.5 c	2.8
	0.1-0.7	0.1-2.4	1.0-6.0
C-peptide increment 5 min (pmol/l)	367 c	342 c	852
	42-1559	76-947	368-2265

Median (range);
* p<0.05, # p<0.01 compared to baseline;
a p<0.05, b p<0.01, c p<0.001 compared to controls

Table 3. Effects of 6 months insulin therapy on lipid parameters in the 20 non-obese patients.

	before	insulin	controls
NEFA (mmol/l)	0.92 ± 0.39^{c}	$0.59 \pm 0.23^{\#}$	0.44 ± 0.12
LDL-cholesterol (mmol/l)	3.54 ± 1.06^{b}	$3.22 \pm 0.97^{*}$	2.76 ± 0.66
HDL-cholesterol (mmol/l)	0.93 ± 0.25^{a}	0.95 ± 0.36^{a}	1.26 ± 0.46
LDL/HDL-cholesterol ratio	3.95 ± 1.36^{c}	$3.59 \pm 1.28^{*b}$	2.45 ± 0.91
Triglycerides (mmol/l)	1.85 ± 0.80^{c}	$1.45 \pm 0.43^{*b}$	1.01 ± 0.35
VLDL-triglycerides (mmol/l)	1.07 ± 0.50^{c}	$0.65 \pm 0.29^{\#}$	0.63 ± 0.20

Mean ± SD;
* $p<0.05$, $^{\#}$ $p<0.01$ compared to baseline;
^{a} $p<0.05$, ^{b} $p<0.01$, ^{c} $p<0.001$ compared to controls

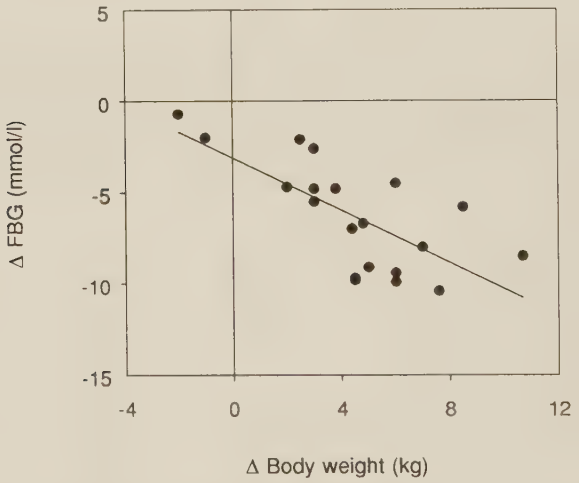

Figure 1. Changes in body weight are significantly ($r=-0.75$, $p<0.01$) related to changes in fasting blood glucose levels (FBG) after 6 months insulin therapy in 20 non-obese patients with type 2 diabetes mellitus, failing on oral therapy.

Islet B-cell function

After 6 months of insulin therapy there was a significant increase in fasting ($p<0.01$) and post-breakfast ($p<0.05$) levels of plasma insulin. No changes in the various parameters of islet B-cell function were observed.

Lipids

The effects of therapy on the parameters of lipid metabolism are given in table 3. There was a significant decrease in plasma LDL-cholesterol, the LDL/HDL-cholesterol ratio, as well as NEFA, total and VLDL-triglycerides. LDL-cholesterol, VLDL-triglycerides and NEFA reached levels comparable to values, found in non-diabetic individuals. No significant correlation was found between the improvement in blood glucose control or the increase in plasma insulin levels, and the changes in the various lipid parameters.

Obese patients

Figure 2 shows the course of blood glucose and HbA_1 in the six obese patients. At the start of insulin treatment they were less hyperglycaemic than the non-obese: fasting blood glucose 11.3 ± 2.2 mmol/l, postprandial blood glucose 14.8 ± 1.9 mmol/l, and HbA_1 10.7 ± 1.1%. Insulin dose after 6 months was 44 ± 18 (range 20-78) U. Body weight did not change significantly: two patients managed to lose some weight while on insulin, whereas two patients gained 3.0 and 4.8 kg, respectively. Fasting blood glucose after 6 months was 8.8 ± 2.7 mmol/l, post-prandial blood glucose was 13.2 ± 2.8 mmol/l, and HbA_1 was 9.8 ± 1.3%. One patient (BMI 30.4 kg/m^2) showed a clear deterioration of blood glucose control. Fasting C-peptide decreased in all patients (median value from 849 to 253 pmol/l); fasting and postprandial plasma insulin levels did not change significantly. Results of glucagon-tests and plasma lipids were available in 5 of the 6 patients. C-peptide AUC decreased in 4 of these 5 (from 5.0 to 2.6 nmol/l.15min). HDL-cholesterol increased in 4 of the 5 patients, from 1.07 ±

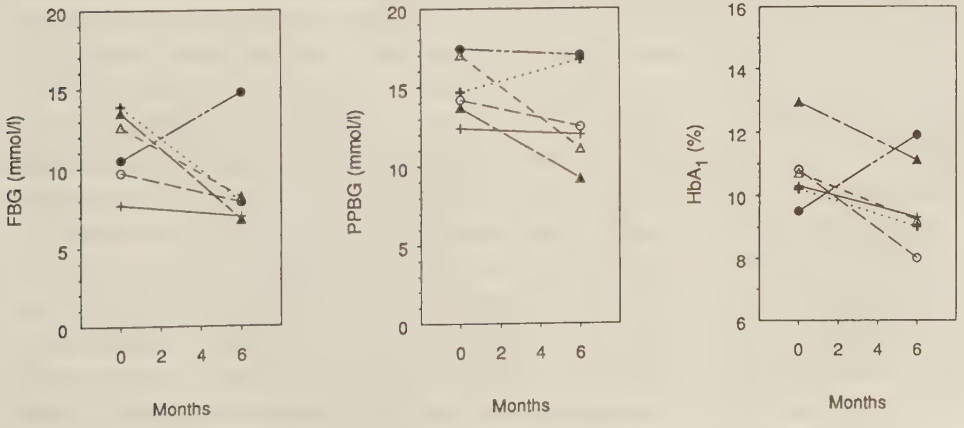

Figure 2. Changes in fasting (FBG) and postprandial blood glucose (PPBG), and HbA_1 after 6 months insulin therapy in 6 obese patients with type 2 diabetes mellitus, failing on oral therapy.

0.19 to 1.16 ± 0.28 mmol/l. Due to the small number of observations these changes were not statistically significant. The other lipid parameters did not change.

History

Almost all patients experienced an improvement in well-being, together with a decrease in symptoms of hyperglycaemia. One non-obese patient experienced one episode of hypoglycaemia, necessitating medical assistance. He recovered without sequelae after intravenous administration of glucose.

DISCUSSION

Our non-obese patients with secondary failure to oral hypoglycaemic agents had normal fasting insulin and C-peptide levels, compared to control subjects. However, these are insufficient, when the level of fasting blood glucose was taken into account. After stimulation with glucagon, insulin secretory capacity proved to be greatly diminished compared to control subjects. Hence, these patients can be classified as 'insulin deficient' (21), and they need insulin to achieve good metabolic control ('insulin requiring'). In the present study, a simple regimen comprising twice-daily insulin injections significantly improved blood glucose control. The improvement of blood glucose control in the individual patient was directly correlated with the increase in body weight, that was observed in these patients. This implies that more severe hyperglycaemia reflects a more catabolic state, which is reversed by insulin therapy. Almost all patients reported improved well-being, and disappearance of hyperglycaemic symptoms. Such symptoms often were previously not recognized as such. No severe complications of insulin therapy were seen. Only one episode of severe hypoglycaemia, demanding medical assistance, was witnessed. Although blood glucose control was greatly improved, seven patients did not reach the desired level of glycaemia. It was not possible to identify these patients prior to the start of insulin treatment on basis of duration of diabetes, islet B-cell function, body weight or age, in comparison with well-controlled diabetic patients. In such patients more intensive efforts are needed, for instance multiple injection regimes and repeated education and instruction in self-regulation, to achieve optimal blood glucose control. In 5 of the 6 obese patients a similar improvement in blood glucose control was achieved, without significant increase in body weight. Thus, obesity does not seem to be a contraindication for institution of

insulin treatment, when therapy with oral hypoglycaemic agents does not result in adequate control.

Various insulin administration schemes have been advocated in diabetic patients with secondary failure to oral hypoglycaemic agents. Once-daily regimens employing long-acting insulin have been shown to improve glycaemic control in severely hyperglycaemic patients, but they often fail to normalize fasting and postprandial hyperglycaemia, and even may produce significant hypoglycaemias in the afternoon or during the night (14,15). A basal insulin supplement was shown to normalize fasting blood glucose in 15 patients (obese and non-obese) with varying levels of blood glucose control, but such normalization did not always result in near-normal HbA_1 levels (23). Although it was suggested that achieving normal fasting blood glucose levels in type 2 diabetic patients is more important than control of postprandial hyperglycaemia (15,23), no epidemiologic studies support this 'concept'. We feel that maintaining near-normoglycaemia throughout the day while avoiding the risk of hypoglycaemias is warranted, because of the relationship between mean level of glycaemia (HbA_1) and the occurrence of (micro)vascular complications (7,24-26). In the non-obese patients lipid metabolism had improved significantly after 6 months insulin therapy. Previous studies on the effects of insulin treatment and the resulting improvement in blood glucose control on lipid metabolism have yielded controversial results (27). As in our patients, correction of hyperglycaemia per se was shown to reduce triglyceride levels. This was explained by enhanced catabolic rate and decreased production of VLDL (27). In agreement with earlier reports (28), we did not find changes in HDL-cholesterol levels. However, insulin therapy was shown to enhance HDL_2-cholesterol levels in type 2 diabetic patients failing to sulphonylurea therapy (29). In our patients, no correlation was found between the improvement of the various lipid parameters and changes in fasting blood glucose, HbA_1, or fasting or post-prandial insulin levels in our patients.

We conclude that insulin therapy in type 2 diabetic patients failing on sulphonylurea therapy greatly improved blood glucose control with a slight improvement of lipid profile. Twice-daily administration of intermediate-acting or a mixture of fast- and intermediate-acting insulin can be safely instituted on an outpatient base as first regimen in such patients. In the majority of patients this regimen can optimize blood glucose control. More complicated regimens, such as multiple daily injections or combination of insulin and oral hypoglycaemic agents may be warranted in the younger type 2 diabetic patients, in whom the twice-daily regimen fails to restore adequate control.

REFERENCES

1. Skyler JS. Non-insulin-dependent diabetes mellitus: a clinical strategy. Diabetes Care 1984; 7 (suppl. 1): 118-129.
2. Wolffenbuttel BHR, Weber RFA, Koetsveld PM van, Verschoor L. Limitations of diet therapy in non-insulin dependent diabetes mellitus. Int J Obesity 1989; 13: 173-182.
3. DeFronzo RA, Ferrannini E, Koivisto V. New concepts in the pathogenesis and treatment of noninsulin-dependent diabetes mellitus. Am J Med 1983; 74 (suppl): 52-81.
4. Hadden DR, Blair ALT, Wilson EA *et al.* Natural history of diabetes presenting age 40-69 years: a prospective study of the influence of intensive dietary therapy. Quart J Med 1986; 59: 579-598.
5. Gerich JE. Sulfonylureas in the treatment of diabetes mellitus. Mayo Clin Proc 1985; 60: 439-443.
6. Groop LC, Pelkonen R, Koskimies S, Bottazzo GF, Doniach D. Secondary failure to treatment with oral antidiabetic agents in non-insulin-dependent diabetes. Diabetes Care 1986; 9: 129-133.
7. Heine RJ. Insulin treatment of non-insulin-dependent diabetes mellitus. In: Baillière's Clinical Endocrinology and Metabolism, Non-insulin-dependent diabetes. Nattrass M, Hale PJ, Eds. London, 1988.
8. Garvey WT, Olefsky JM, Griffin J, Hamman RF, Kolterman OG. The effect of insulin treatment on insulin secretion and insulin action in type II diabetes mellitus. Diabetes 1985; 34: 222-234.
9. Ginsberg H, Rayfield EJ. Effect of insulin therapy on insulin resistance in type II diabetic subjects-evidence for heterogeneity. Diabetes 1981; 30: 739-745.
10. Stout RW. The role of insulin in atherosclerosis in diabetics and nondiabetics. Diabetes 1981; 30 (suppl 2): 54-57.
11. Tattersall RB. Diabetes in the elderly - a neglected area? Diabetologia 1984; 27: 167-173.
12. Tattersall RB, Scott AR. When to use insulin in the maturity onset diabetic. Postgrad Med J 1987; 63: 859-864.
13. Riddle MC, Hart JS. Which patients might benefit from combining a sulfonylurea with insulin? (letter) Diabetes Care 1985; 8: 205.
14. Roland JM, Lewin IG, O'Brien AD, Markanday S, Kurtz AB, Corrall RJM. A comparative study of once daily insulin injection regimes in the treatment of elderly diabetics. Diabetes Res 1987; 4: 131-134.
15. Tindall H, Bodansky HJ, Stickland M, Wales JK. A strategy for selection of elderly type 2 diabetic patients for insulin therapy, and a comparison of two insulin preparations. Diabetic Med 1988; 5: 533-536.
16. WHO Expert Committee on Diabetes Mellitus. Technical Report Series 727, 1985. Geneva: World Health Organization.
17. Poulsen S, Billesbolle P, Kolendorf K, Thorsteinsson B. The C-peptide response to glucagon injection in IDDM and NIDDM patients. Horm Metabol Res 1985; 17: 39-40.
18. Heding LG. Radioimmunological determination of human C-peptide in serum. Diabetologia 1975; 11: 541-548.
19. Laurell S, Tibbling G. Colorimetric micro-determination of free fatty acids in plasma. Clin Chim Acta 1967; 16: 57-62.

20. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and b-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-419.
21. Ward WK, Bolgiano DC, McKnight B, Halter JB, Porte Jr D. Diminished B cell secretory capacity in patients with non-insulin-dependent diabetes mellitus. J Clin Invest 1984; 74: 1318-1328.
22. Bogardus C, Lillioja S, Howard BV, Reaven GM, Mott D. Relationships between insulin secretion, insulin action, and fasting plasma glucose concentrations in nondiabetic and non-insulin-dependent diabetic subjects. J Clin Invest 1984; 74: 1238-1246.
23. Holman RR, Steemson J, Turner RC. Sulphonylurea failure in type 2 diabetes: treatment with a basal insulin supplement. Diabetic Med 1987; 4: 457-462.
24. Unger RH. Meticulous control of diabetes: benefits, risks and precautions. Diabetes 1982; 31: 479-483.
25. Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4400 patients observed between 1947 and 1973. Diabetes Care 1978; 1: 168-188 and 252-263.
26. Singh BM, Rutter JD, Fitzgerald MG. The natural history of non-insulin-dependent diabetes mellitus. In: Baillière's Clinical Endocrinology and Metabolism, Non-insulin-dependent diabetes. Nattrass M, Hale PJ, Eds. London, 1988.
27. Reaven GM. Abnormal lipoprotein metabolism in non-insulin-dependent diabetes mellitus. Am J Med 1987; 83 (suppl.3A): 31-40.
28. Hollenbeck CB, Chen Y-DI, Greenfield MS, Lardinois CK, Reaven GM. Reduced plasma high density lipoprotein-cholesterol concentrations need not increase when hyperglycemia is controlled with insulin in non-insulin-dependent diabetes mellitus. J Clin Endocrinol Metabol 1986; 62: 605-608.
29. Razenberg PPA, Venekamp WJRR, Sikkenk AC, Heine RJ, van der Veen EA. Effects of insulin treatment in type II diabetes on insulin sensitivity and insulin responsiveness. Diab Res Clin Pract 1985; 1 (suppl.1): 465.

CHAPTER 8

Combination of insulin and sulphonylurea in patients with type 2 diabetes mellitus and failure on oral therapy

The effects of different treatment regimens

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SUMMARY

We compared the effects of different insulin-administration schemes on glucose and lipid-metabolism in 52 patients with type 2 diabetes (mean ± SD age 69 ± 9 years, body mass index 25.7 ± 5.5 kg/m^2, median time since diagnosis of diabetes 9 (range 1-34) years, 21 males), who were poorly controlled despite diet and maximal doses of oral hypoglycaemic agents. Twice-daily insulin injections (scheme A) were compared with regimens of once-daily insulin (before breakfast, scheme C, or at bedtime, scheme B) in combination with glibenclamide. So far, 47 patients have completed the study. Five patients in regimen B and 4 patients in group C required a second injection of insulin. Almost all patients reported improved well-being and diminished hyperglycaemic complaints. No severe hypoglycaemias were observed. Body weight increase was moderate (mean +4.2 kg). In the whole group of patients, fasting blood glucose decreased from 14.6 ± 2.3 mmol/l to 8.5 ± 2.2 mmol/l ($p<0.001$), and HbA_{1c} fell from 10.9 ± 1.4% to 8.1 ± 1.4% ($p<0.001$). Twenty-one patients reached HbA_{1c} levels below 8.0%, and 17 below 7.5%. Patients on regimen A reached the best improvement of blood glucose control, the decrease of fasting and mean blood glucose was 42% and 49%, respectively, while HbA_{1c} decreased by 27%. They injected, however, the largest amount of insulin (mean 42U). Both in patients on insulin alone and in those treated with insulin + glibenclamide, significant increases of HDL-cholesterol were observed (from 1.10 ± 0.31 to 1.24 ± 0.32 mmol/l, and from 1.03 ± 0.27 to 1.14 ± 0.32 mmol/l, respectively). Further, plasma triglycerides and non-esterified fatty acids decreased significantly. Total cholesterol decreased only in the patients treated with insulin alone (from 7.08 ± 1.42 to 6.26 ± 1.15 mmol/l, $p<0.01$). Apolipoproteins AI, AII and B did not show any significant changes. We conclude that therapy with twice-daily insulin injections markedly improved blood glucose control and plasma lipids. Combination of insulin with glibenclamide resulted with an equal improvement of metabolic control, with lower doses of insulin, but with less improvement of plasma lipids. The increase of HDL-cholesterol without concomitant increase of apolipoproteins AI and AII suggests enrichment of the HDL-particle with cholesterol during insulin therapy.

INTRODUCTION

Patients with type 2 diabetes mellitus are usually treated with diet in combination with oral hypoglycaemic agents, when diet therapy alone fails to normalize glucose metabolism (1-3). Some patients do not achieve adequate control with such therapy. Insulin treatment is the available option (4,5). Insulin therapy may diminish hyperglycaemic complaints and improve blood glucose control. It was also shown previously that intensive insulin therapy can improve islet B-cell function and peripheral insulin action (6). However, especially in the obese patients weight gain may pose a problem. Further, the resulting peripheral hyperinsulinemia might be of importance, since increased plasma insulin levels are considered to be an independent risk factor for the development of atherosclerosis (8,9). In addition, the incidence of hypoglycaemias during this therapy is reported to be greater than during oral therapy (10).

Various insulin regimens have been proposed (5). Although twice-daily administration (before breakfast and diner) is frequently advocated, many physicians rely on only one injection in the morning, often because patient acceptance of insulin therapy is thought to be better with one injection. During the last few years interest in the combination of insulin with sulphonylurea therapy has revived (11). Such a combination might be beneficial, by reducing the dose of insulin needed, and thus possibly diminishing the degree of peripheral hyperinsulinaemia. The injection of intermediate-acting insulin at bedtime, together with daytime sulphonylurea use, was especially advocated (12). By this way excessive hepatic glucose production, which is dominant during evening and night and leads to pronounced fasting hyperglycaemia, should be suppressed almost completely. Weight gain might be less with this therapy. However, negative results of combined therapy on HDL-cholesterol have been described (13).

In this study, we compared the effect of three insulin-administration schemes on glucose and lipid-metabolism in patients with type 2 diabetes, who are poorly controlled with maximal doses of oral hypoglycaemic agents. The results obtained in the first 52 patients are presented.

MATERIALS AND METHODS

Patients

Until now, 52 patients (mean ± SD age 69 ± 9 years, body mass index, BMI 25.7 ± 5.5 kg/m^2, median time since diagnosis of diabetes 9 (range 1-34) years, 21 males) with type 2 diabetes according to the WHO-criteria (14) entered the study. All were poorly controlled despite diet and maximal doses of oral hypoglycaemic agents (15 mg glibenclamide daily, or -in some patients- glibenclamide with metformin). Poor blood glucose control was defined as a fasting blood glucose concentration (mean of last 3 measurements within 2 months) above 8.0 mmol/l. A complete history and physical examination was performed to exclude intercurrent illness or cardiac, hepatic, renal or other endocrine disease. No patient had severe hypertension (diastolic blood pressure above 110 mmHg), severely impaired kidney function (serum creatinine above 140 µmol/l, or creatinine-clearance below 40 ml/min), or was treated with corticosteroids. All patients gave their informed consent before participating. The study was approved by the Ethical Committee of the Maastricht University Hospital.

Study-design

During a run-in period of at least 3 months oral therapy was continued, dietary treatment optimized, and instruction in self-monitoring of blood glucose -if possible- and insulin injections, as well as formal diabetes education, were given. The patients were block-randomized to three different treatment regimens for 6 months:

Regimen A: twice-daily (before breakfast and dinner) administration of NPH-insulin (Protaphane HM) using a pen-device (Novopen I or II). When postprandial blood glucose values exceeded 10.0 mmol/l, fast-acting insulin (Actrapid HM) was supplemented. For this purpose a mixture of 30:70 Actrapid/Protaphane (Actraphane) was used.

Regimen B: combination of NPH-insulin, administered at bedtime, with glibenclamide during the day (10 mg at breakfast and 5 mg at dinner). When blood glucose values during the day consistently exceeded 10.0 mmol/l, a second injection of NPH-insulin before breakfast was added.

Regimen C: combination of NPH-insulin once daily, administered before breakfast, in combination with glibenclamide during the day (10 mg at breakfast and 5 mg at dinner). When postprandial blood glucose values during the day consistently exceeded 10.0 mmol/l, actraphane was used instead. When post-

dinner blood glucose levels exceeded 10.0 mmol/l, a second injection of NPH-insulin before dinner was added.

Insulin dose was adjusted on the base of blood glucose measurements made at home by the patients. Goals of therapy were fasting blood glucose levels <7.0 mmol/l, and postprandial blood glucose values below 10.0 mmol/l, and HbA_{1c} levels below 8.0%.

Measurements

At baseline, blood was drawn for the determination of glycosylated haemoglobin (HbA_{1c}), serum fructosamine, non-esterified fatty acids (NEFA), plasma lipids, and apolipoproteins. Islet B-cell function was assessed after an overnight fast by measuring fasting plasma insulin and C-peptide levels, as well as plasma C-peptide levels 5, 10, 15 and 30 min after injection of 1 mg glucagon.

Follow up

All patients visited the outpatient clinic 2 and 4 weeks after beginning insulin therapy, and thereafter monthly, when measurements of body weight, glucose profile, HbA_{1c} and serum fructosamine were made. They were asked to measure their blood glucose at home once a week (morning, before lunch, before dinner, evening) using a reflectance meter (Glucometer II, Bayer-Ames, FRG). After six months baseline measurements were repeated.

For comparison, glucagontests and lipid determinations were performed in non-obese control subjects.

Analytical procedures

Blood glucose was measured in venous whole blood with an automated hexokinase method. Serum fructosamine was determined according to Johnson *et al.* (15) after alkalinising and reduction with nitroblue tetrazolium (Sigma) on the Cobas Bio analyser. Calibration was performed with 1-desoxy-1-morfolino-fructose (Sigma) in a albumin solution. The reference values of this assay were lower than those of the widely-used Fructosamine Roche kit, due to the use of a different standard and reductor. Comparison with the Roche kit was excellent ($r=0.98; y=1.16x+2$, $p<0.001$). Between-assay coefficient of variation of our fructosamine determination is 4%. HbA_{1c} was determined with HPLC (DIA-MAT, Bio-Rad Laboratories, Richmond, Ca., USA). Normal values were 4.4-6.2%, between-assay cv was 2.6%. Plasma free insulin levels (IRI) were analyzed with radio-immunoassay (Pharmacia, Uppsala, Sweden) after poly-

ethyleneglycol pretreatment, and plasma C-peptide was measured with radioimmunoassay (Mallinckrodt, FRG). Between-assay variation of insulin-RIA was 7.5%, and C-peptide 9%. Cholesterol (CHOD-PAP, Boehringer, Mannheim, FRG) and triglycerides (Triglycerid Rapid, Roche, Switzerland) were determined with enzymatic methods. HDL-cholesterol was measured after precipitation of VLDL and LDL with PEG 6000. Apolipoproteins AI, AII and B were determined with an immunoturbidimetric assay (Boehringer, Mannheim, FRG) on a Cobas Bio analyser. Intra- and interassay coefficient of variation were 1.9 and 6.9%. Normal values of the apolipoproteins AI, AII and B for normolipidaemic males are 125 ± 22, 42 ± 6 and 77 ± 16 mg/dl, respectively, and for females 139 ± 25, 42 ± 6 and 76 ± 15 mg/dl.

Calculations and statistical analyses

Beta-cell function (BCF) was assessed in three ways:

1. as the release of C-peptide after i.v. injection of 1 mg glucagon, calculated as the incremental area under the curve (C-peptide AUC);
2. from the fasting levels of blood glucose (FBG), insulin (FIRI) and C-peptide (FCP), by calculating the formulae of Matthews (16);
3. as the level of C-peptide 5 min after glucagon injection ($C\text{-peptide}_{5min}$).

All data are expressed as mean ± SD, or median and range, when not normally distributed. Calculations were performed with the SPSS/PC+ version 3.1 statistical software package (SPSS Inc, Chicago, IL, USA). Group differences in base-line variables were compared by one-way analysis of variance for continuous variables and chi-square tests for categorical variables. Student-Newman-Keuls test was applied to correct for multiple comparisons. Changes of blood glucose control between the treatment groups (HbA_{1c}, serum fructosamine, fasting and mean blood glucose) and lipid variables were compared by analysis of variance; when the changes were not normally distributed, Kruskal-Wallis analysis of variance was used. Linear regression analysis was used to determine the relationship between two variables. P-values below 0.05 were considered statistically significant.

RESULTS

Baseline data

Body mass index (BMI) was significantly higher among females (27.3 ± 5.9 *vs.* 23.2 ± 3.7 kg/m^2, p=0.008). The degree of blood glucose control was similar between both sexes. Females had higher levels of fasting plasma C-peptide (964 ± 518 *vs.* 626 ± 289 pmol/l, p=0.0094), insulin (94 ± 56 *vs.* 59 ± 23 pmol/l, p=0.0103), as well as parameters of islet B-cell function (calculated islet B-cell function, C-peptide AUC, and C-peptide$_{5min}$), whereas lipid variables were comparable.

When patients older than 70 years were compared with those under 70 years, no differences were found in blood glucose control, islet B-cell function and plasma lipids, although duration of diabetes was longer in the older age group (15 *vs.* 9 years, p=0.0011), while BMI was lower (23.8 ± 4.2 *vs.* 27.2 ± 6.1 kg/m^2, p=0.0262).

The baseline data of all patients in the initial treatment groups are listed in tables 1 and 2. Patients in group 2 were slightly younger, and had a shorter known duration of diabetes. Patients in group 1 had lower body mass index. All other variables were similar between the 3 groups. No differences in islet B-cell function or plasma lipids were observed.

Table 1. Demographic variables and blood glucose control at baseline in the 3 treatment groups.

	Group 1 n=23	Group 2 n=15	Group 3 n=14	Controls n=18
Age (years)	70 ± 9	63 ± 9*	73 ± 6	—
Male/female	11/12	5/10	5/9	9/9
Known duration of diabetes (years)	9 (1-34)	6 (2-15)*	14 (6-27)	0
Body mass index (kg/m^2)	23.6 ± 4.6#	27.7 ± 6.5	26.9 ± 4.8	—
Fasting blood glucose (mmol/l)	14.5 ± 1.5	14.9 ± 2.1	14.1 ± 3.3	4.1 ± 0.3
Mean blood glucose (mmol/l)	17.8 ± 2.5	17.0 ± 2.6	17.8 ± 3.3	4.5 ± 0.4
Serum fructosamine (mmol/l)	2.17 ± 0.59	1.85 ± 0.27	1.99 ± 0.47	—
Glycosylated haemoglobin (%)	11.3 ± 1.3	10.5 ± 1.2	10.9 ± 1.6	5.2 ± 0.5

Data are shown as mean ± SD,
* p<0.05 compared to both other groups, # p<0.05 compared to group 2.

Table 2. Islet B-cell function and lipid variables at baseline in the 3 treatment groups.

	Group 1 n=22	Group 2 n=15	Group 3 n=14	Controls n=18
Fasting plasma C-peptide	615	888	870	551
(pmol/l)	190-1990	385-2350	530-2285	370-820
Fasting plasma insulin	64	75	67	46
(pmol/l)	26-151	37-212	47-286	32-66
C-peptide5 min	975	1440	1320	1759
(pmol/l)	330-2540	600-3000	550-4260	1240-2620
C-peptide AUC	4.9	5.6	7.9	29.8
(nmol/l.30min)	1.58-18.55	1.20-18.61	0.72-32.59	19.8-45.1
C-peptide AUC/blood glucose	346	348	621	7345
	115-1262	91-1604	44-2217	5016-10620
BCF C-peptide	16	26	24	150
(%)	4-48	10-49	11-55	100-312
BCF insulin	16	18	20	120
(%)	5-42	10-44	11-69	84-159
Non-esterified fatty acids (mmol/l)	1.00 ± 0.31	1.04 ± 0.39	1.09 ± 0.36	0.48 ± 0.12
Total cholesterol (mmol/l)	7.1 ± 1.4	6.3 ± 1.4	6.1 ± 1.4	5.0 ± 0.4
HDL-cholesterol (mmol/l)	1.09 ± 0.31	1.03 ± 0.27	1.02 ± 0.28	1.40 ± 0.29
Triglycerides	2.41	1.72	1.98	1.50
(mmol/l)	1.11-11.4	0.83-9.09	1.04-6.41	0.51-2.00

Data are shown as mean ± SD, or median (range)

Follow-up after 6 months

Of the 52 patients, 47 were fully evaluable after 6 months. One patient died four months after the start of insulin therapy due to a myocardial infarction. Two patients withdrew because of intercurrent diseases, while 2 patients did not yet complete the 6 months study period. Five patients in regimen B required a second injection of insulin because of marked daytime hyperglycaemia, whereas 4 patients on regimen C required an additional pre-dinner injection of insulin because of significant hyperglycaemia in the evening.

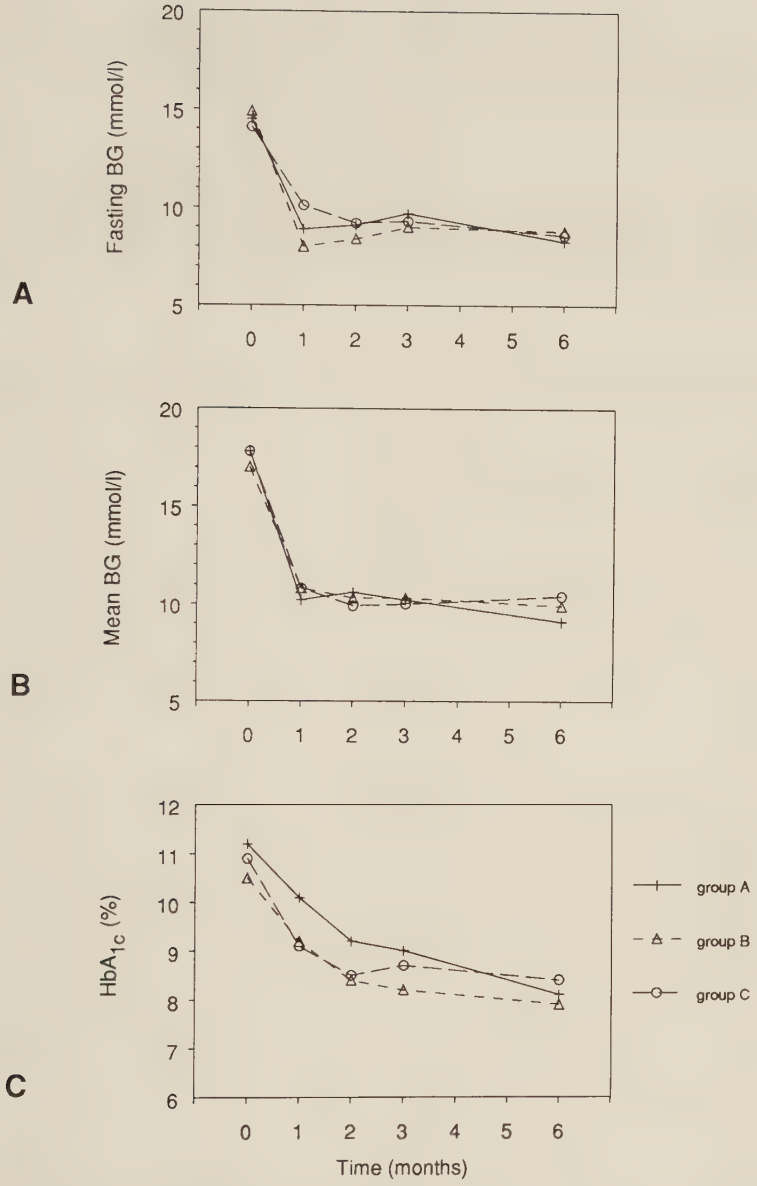

Figure 1. Course of fasting (A) and mean blood glucose (B) and HbA_{1c} (C) in the different treatment groups.

Patients who initially started with 1 injection, and had to switch to the 2-injection regimen, showed lower fasting plasma C-peptide (median 725 *vs.* 900 pmol/l) and insulin levels (median 63 *vs.* 79 pmol/l) before insulin treat-

ment compared to patients who continued with 1 injection. Also, C-peptide response after glucagon was lower (4.5 *vs.* 8.7 nmol/l.30min).

Well-being

Almost all patients reported improved well-being and diminished hyperglycaemic complaints, like thirst, polyuria and excessive nocturnal urine production. No severe hypoglycaemias, necessitating medical assistance, were observed.

Table 3. Pre-treatment levels, and the mean of the absolute and percentual changes in body weight and variables of blood glucose control after 6 months treatment with insulin (+/- sulphonylurea).

	Regimen A (n=22)	Regimen B (n=13)	Regimen C (n=12)
Patients with 2 injections	22	5	4
Insulin dose 6 months (U)	42 ± 12	24 ± 11 $^{\$}$	27 ± 18 $^{\$}$
Body weight (kg)	66 ± 13	78 ± 17 $^{\$}$	68 ± 12
absolute change	+4.2 $^{\&}$	+4.1 $^{\#}$	+3.7 $^{\#}$
percentage change	+6.6	+5.3	+5.5
Fasting blood glucose (mmol/l)	14.6 ± 1.5	15.8 ± 2.0	13.6 ± 3.2
absolute change	-6.2 $^{\&}$	-6.0 $^{\&}$	-5.8 $^{\#}$
percentage change	-42	-40	-39
Mean blood glucose (mmol/l)	17.9 ± 2.5	17.6 ± 3.7	17.3 ± 3.0
absolute change	-8.8 $^{\&}$	-6.8 $^{\#}$	-7.4 $^{\&}$
percentage change	-49	-40	-41
Serum fructosamine (mmol/l)	2.17 ± 0.61	1.78 ± 0.23	1.96 ± 0.56
absolute change	-0.89 $^{\&}$	-0.50 $^{\#}$	-0.58 $^{\#}$
percentage change	-38	-26	-24
Glycosylated haemoglobin (%)	11.4 ± 1.3	10.8 ± 1.4	10.3 ± 1.5
absolute change	-3.2 $^{\&}$	-2.5 $^{\#}$	-2.4 $^{\#}$
percentage change	-27	-23	-22
Number of patients attaining HbA_{1c} level < 8.0%	10	7	4

$^{\&}$ $p<0.001$, $^{\#}$ $p<0.01$ compared to baseline, $^{\$}$ $p<0.05$ *vs.* regimen A

Blood glucose control

In the whole group of patients fasting blood glucose decreased from 14.6 ± 2.3 to 8.5 ± 2.2 mmol/l ($p<0.001$), and HbA_{1c} fell from 10.9 ± 1.4 to 8.1 ± 1.4% ($p<0.001$). Twenty-one patients reached HbA_{1c} levels below 8.0%, and 17 levels below 7.5%, which is 4 times the upper limit of normal of our assay. In the patients treated with one insulin injection daily, mean insulin dose after 6 months was lower compared to the patients on regimen A (table 3). These

Table 4. Pre-treatment levels and mean changes in measures of plasma lipids after 6 months insulin therapy.

	Regimen A (n=22)	Regimen B-C (n=25)
Non-esterified fatty acids (mmol/l)	1.01 ± 0.32	1.09 ± 0.34
absolute change	-0.36 &	-0.56 &
percentage change	-34	-51
Cholesterol (mmol/l)	7.1 ± 1.4	6.4 ± 1.4
absolute change	-0.8 #	-0.4
percentage change	-10	-5
HDL-cholesterol (mmol/l)	1.10 ± 0.31	1.03 ± 0.27
absolute change	0.14 #	0.10 *
percentage change	15	11
Triglycerides (mmol/l)	2.42	2.04
	1.25-11.4	0.82-9.1
absolute change	-1.19 &	-0.78 #
percentage change	-33	-21
Apolipoprotein AI (mg/dl)	114 ± 19	110 ± 18
absolute change	+5	+2
relative change	+4	+2
Apolipoprotein AII (mg/dl)	34 ± 5	33 ± 7
absolute change	0	0
relative change	0	0
Apolipoprotein B (mg/dl)	101 ± 26	90 ± 24
absolute change	-12	-2
relative change	-12	-3

* $p<0.05$, # $p<0.01$, & $p<0.001$ compared to pre-treatment

patients on 2 injections (without addition of glibenclamide) reached the best improvement of blood glucose control, the decrease of fasting and mean blood glucose was 42% and 49%, respectively, while HbA_{1c} decreased by 27%.

C-peptide/insulin

When all patients were considered together, fasting C-peptide levels decreased significantly by a mean of 25% after 6 months insulin therapy (from 835 ± 459 pmol/l to 611 ± 387 pmol/l, $p<0.001$), while fasting insulin levels were 40% higher (102 ± 48 pmol/l *vs.* 80 ± 51 pmol/l, $p=0.003$). A comparable increase in fasting insulin levels was observed in all treatment groups.

Plasma lipids

Both in patients on insulin alone and in those treated with insulin+glibenclamide, significant increases of HDL-cholesterol were observed (from 1.10 ± 0.31 to 1.24 ± 0.32 mmol/l, and from 1.03 ± 0.27 to 1.14 ± 0.32 mmol/l, respectively). Further, plasma triglycerides and non-esterified fatty acids decreased significantly (table 4). Total cholesterol decreased in the patients treated with insulin only (from 7.08 ± 1.42 to 6.26 ± 1.15 mmol/l, $p<0.01$). Apolipoproteins AI, AII and B did not show any significant changes.

DISCUSSION

The interim-analysis of our study shows the effectiveness of insulin therapy, alone or in combination with glibenclamide, to improve blood glucose control in type 2 diabetic patients with secondary failure to treatment with oral hypoglycaemic agents. In all 3 treatment groups a clear decrease of fasting and mean daily blood glucose, and of glycosylated haemoglobin was observed. The decrease of these measures was the largest in group A patients, treated with twice-daily insulin injections alone. However, insulin dose was also the highest in these patients, compared to the 2 groups who were treated with insulin combined with glibenclamide.

Of the patients, who were initially randomized for once-daily insulin injections in combination with glibenclamide, 9 (36%) did not reach adequate improvement of metabolic control, and needed a second insulin injection. In the patients starting with bedtime insulin, this decision was made when fasting blood glucose levels were near-normal, but postprandial blood glucose levels

exceeded 12 mmol/l; in the patients with morning insulin a second injection was added when evening blood glucose levels were unacceptably high.

Only in regimen A patients a significant decrease of total plasma cholesterol was observed, whereas triglycerides and NEFA decreased significantly, both in patients on insulin only and in patients treated with combined therapy. Also in both groups an increase of HDL-cholesterol was observed. However, total cholesterol and triglyceride levels remained elevated, and HDL-cholesterol remained lower compared to non-diabetic subjects, as was already demonstrated by others (17,18). The increase of HDL-cholesterol without concomitant increase of apolipoproteins AI and AII suggests enrichment of the HDL-particle with cholesterol during insulin therapy. Our findings are in contrast with observations made by Stenman *et al* (13). They reported that during combined therapy HDL-cholesterol was significantly lower than with insulin alone. These observations were made in only 15 patients, who were treated with insulin alone (most of them only 1 injection), or insulin in combination with glibenclamide in a 4-month cross-over study. It is, however, difficult to draw firm conclusions on their findings, since the number of patients was rather low. The present study shows more positive results, but is still continuing, and more definite evaluations of the effects of combined therapy on plasma lipids will be made when an even larger number of patients has been studied.

Secondary failure to oral hypoglycaemic agents after an initial favourable response may occur in approximately 5-10% of patients on a yearly basis (19,20). Insulin treatment is then the available option. It was shown previously that intensive insulin therapy improves insulin secretory capacity of the B-cells, enhances peripheral insulin action and suppresses excessive hepatic glucose production (6,7,21). However, especially in the obese patients weight gain on insulin therapy can pose significant problems. Further, the resulting peripheral hyperinsulinaemia may be of importance, since increased plasma insulin levels are considered to be an independent risk factor for the development of atherosclerosis. Average increase of fasting insulin levels in our total patient group was 40%. However, acceleration of diabetic complications due to (severe) hyperglycaemia in poorly controlled patients is in our view more relevant than the theoretical disadvantage of hyperinsulinaemia.

Groop *et al* (20) studied possible factors influencing secondary drug failure to treatment with oral hypoglycaemic agents. They reported that patients failing to sulphonylureas had a lower relative body weight, and lower basal and post-glucagon plasma C-peptide concentrations than patients who were well controlled. There was not a critical C-peptide level discriminating between nonresponders and responders. The reported lower C-peptide levels, however, existed in the presence of higher blood glucose values (13.9 ± 0.4 mmol/l in

nonresponders, against 7.1 ± 0.2 mmol/l in responders). It is known that the level of glycaemia affects the measured basal C-peptide and the C-peptide increase after stimulation: higher blood glucose values potentiate the effect of other insulin secretagogues, such as glucagon and arginine. But, even with higher blood glucose levels lower C-peptide levels were found. Thus, calculation of the ratio of C-peptide and glucose might yield a much better discrimination between responders and nonresponders than comparing C-peptide levels alone. In a previous study we measured C-peptide levels before and during 15 min after intravenous injection of 1 mg glucagon in type 2 diabetic patients failing on dietary therapy (22). An incremental area under the response curve of < 5.0 nmol/l.15 min identified those patients, who exhibited better blood glucose control on insulin therapy compared to treatment with sulphonylureas.

Nonresponders to sulphonylureas also have a higher frequency of auto-antibodies against pancreatic islet cells, thyroid microsomes and gastric parietal cells. They also show a lower prevalence of HLA-B7, the frequency of which is reduced in insulin-dependent diabetes, and a higher prevalence of HLA-B8, which is known to be increased in insulin-dependent diabetes. Hence, a subset of patients with specific immunologic characteristics can be determined with a high risk of secondary drug failure and subsequent insulin requirement.

Approximately 30 years ago it was recommended that insulin be combined with sulphonylureas in the treatment of type 2 diabetic patients poorly controlled with insulin alone (23). Thereafter a period followed, in which the sole use of higher doses of insulin was recommended rather than the combination with sulphonylureas (24). The results of the widely-criticized UGDP study, which suggested an increased risk of cardiovascular deaths in patients treated with sulphonylureas (25,26) also contributed to this view. The last 5 years, however, show a revival of the combined therapy, although its usefulness still is debated (5). Table 5 gives a summary of recent publications, in which the combined therapy was studied. A direct comparison between the studies remains difficult, because of the different doses of sulphonylureas, the various doses and administration regimens of insulin that were used, and the varying degree of obesity of the patients who were studied. Hamelbeck and co-workers (27) reported in a randomized double-blind study that patients treated with the combination of insulin and glibenclamide required a lower insulin dose and exhibited better blood glucose control than patients using insulin and placebo. His and other studies clearly demonstrated that, although there are favourable effects of combined therapy, it is in general difficult to attain (near)normoglycaemia in the individual patient. Some studies have reported only transient beneficial effects of combined therapy. Osei *et al* (29) found only a moderate improvement in glycaemic control after 4 and 16 weeks of glibenclamide and insulin in

severely hyperglycaemic patients (fasting blood glucose 15.9 ± 1.5 mmol/l). In addition, the lower glucose increase and higher C-peptide response after 75 g oral glucose load was only apparent at 4 weeks, and had disappeared at 16 weeks. In a shorter observation period of 8 weeks Groop *et al* (30) also noticed that the initial beneficial effect of combined therapy tended to cease with time. Later studies of his group showed that in insulin-treated type 2 diabetic patients addition of glibenclamide resulted in a better blood glucose control than placebo (HbA_1 7.9 ± 0.5 *vs.* 9.6 ± 0.7%) after 4 months, while insulin dose could be reduced by 25%. Fasting and post-meal plasma free insulin levels were not different.

Although the quantitative effects of combined therapy differ between studies, the improvement in blood glucose control and the reduction of insulin requirement seems primarily due to an increase in endogenous insulin secretion. Comparing insulin plus glibenclamide with insulin alone Simonson *et al* (34) did not find changes in basal hepatic glucose production, nor any improvement in the suppression of hepatic glucose production by insulin, or improvement of insulin sensitivity. In contrast, the increase of both basal and glucagon-stimulated C-peptide levels correlated well with the decrease in insulin requirement in their patients using combined therapy. Finally, combining sulphonylurea and insulin was successful only in those patients, who exhibited residual B-cell function, as estimated by fasting and post-glucagon C-peptide levels (36). Also in our patients, those who needed a second insulin injection showed lower fasting plasma C-peptide and insulin levels and C-peptide response after glucagon, thus had lower residual islet B-cell function before the initiation of insulin treatment.

Riddle (12,41,42) advocates the use of a regimen combining bedtime intermediate-acting insulin with daytime sulphonylurea. This approach aims at reducing fasting blood glucose values by suppression of the increased (nocturnal) hepatic glucose production and high nocturnal concentrations of free fatty acids, which may contribute to hepatic insensitivity to insulin and fasting hyperglycaemia. Taskinen *et al* (43) raised the possibility that the improvement in overall glycaemic control by administration of bedtime insulin is related to the suppression of plasma NEFA concentrations. This hypothesis remains to be proven; in contrast, our data show an equal reduction of fasting plasma NEFA concentrations irrespective of the mode of insulin treatment (morning, evening, or twice-daily injections). Other findings suggested that especially nonobese patients with short duration of diabetes might benefit from this regime (42). We conducted a pilot study employing this regime in 8 obese patients (BMI 28.3-43.1 kg/m^2) with secondary failure to sulphonylurea and biguanide therapy. In only four of them near-normalization of blood glucose control of longer dura-

Table 5. Studies on combined insulin-sulphonylurea therapy in non-insulin-dependent diabetes.

Author	Sulphonylurea +daily dose	Patients	Duration of study	Assessment of therapy effect
Hamelbeck (27)	glibenclamide 15 mg	97 secondary failures to SU mean IBW 107%	2-5 weeks parallel	FBG: I+G: 10.8→ 7.8[b] BGP: 12.8→ 8.4[b] I+P: 10.9→ 9.0 11.9→ 9.7 lower insulin dose in glibenclamide group (24 *vs.* 33 U); no difference in fasting C-peptide
Groop (28)	glibenclamide 8 mg	13 newly insulin-treated mean IBW 109%	8 weeks crossover	no difference in body weight or daily insulin dose; slight[a] reduction in FBG and 24-h urine glucose; higher basal and post-glucagon C-peptide
Osei (29)	glibenclamide 5-20 mg	18 insulin-treated mean IBW 129%	16 weeks parallel	FBG: HbA1: I+G: 15.9 → 14.0[a] 10.9 → 9.6[a] I+P: 14.9 → 13.9 10.4 → 10.4 with G increase[a] in fasting C-peptide; lipids: no difference
Groop (30)	glibenclamide 10 mg	13 insulin-treated mean IBW 123%	8 weeks crossover	no difference in body weight or daily insulin dose; glibenclamide: lower FBG and HbA1 after 4 wks, not after 16 wks; tendency to lower HDL-cholesterol when compared with placebo
Lardinois (31)	glibenclamide 20 mg	14 insulin-treated mean BMI 28.3	3 months uncontrolled	FBG 13.9 → 10.8 HbA1c 8.4 → 7.3 increase in 24-hour C-peptide levels[a] and in insulin-stimulated glucose-utilization[b]
Quatraro (32)	gliclazide 40-240 mg	30 insulin-treated mean BMI 28.6	12 months parallel no placebo	FBG: HbA1: daily insulin dose: I+G: 16.1 → 9.2[a] 12.2 → 9.0[a] 90-57 U[a] I: 15.4 →14.6 11.8 → 11.5 88-85 U with gliclazide sign.[a] increase of C-peptide release after glucagon
Longnecker (33)	tolazamide 500-1000 mg	11 insulin-treated mean IBW 147%	8 weeks crossover	FBG 15.1 → 12.2, decrease in 7/11 patients HbA1 12.7 → 12.2, decrease in 5/10 patients increase in fasting and meal-stimulated C-peptide
Simonson (34)	glibenclamide 20 mg	8 insulin-treated mean IBW 131%	2 months uncontrolled	BGP 8.5 → 7.3[a] HbA1 10.3 → 8.0[a] daily insulin dose 72 → 58 U[a] increase[a] of C-peptide release after glucagon; no change in insulin action

Tabel 5. (cont.)

Author	Sulphonylurea +daily dose	Patients	Duration of study	Assessment of therapy effect
Gutniak (35)	glibenclamide 10.5 mg	20 secondary failures to SU	11 months parallel	FBG: (0→3 →11mo.) HbA1c: insulin dose: I+G: 12.9 → 8.0-10.7 11.1 → 9.1 35 U I+P: 12.3 → 8.5-10.9 10.3 → 8.9 55 U mean IBW 121% no difference in C-peptide/glucose ratio; increase in basal and meal-stimulated C-peptide
Castillo (36)	glipizide 30 mg	10 insulin-treated mean IBW 100%	6 weeks no placebo	glipizide: 5 responders, HbA1c 8.6-7.1 5 nonresponders, HbA1c 7.9-8.8 responders showed higher basal and post-glucagon C-peptide levels
Schade (37)	glibenclamide 20 mg	16 insulin-treated mean IBW 132%	4 months	FBG 12.8 ± 2.8 (I+G) *vs.* 14.3 ± 2.4 (I+P)[a] (4 mo.) HbA1c 10.2 ± 2.0 (I+G) *vs.* 10.9 ± 1.2 (I+P)[a] (4 mo.) no difference in insulin dose; higher fasting & post-glucagon insulin levels
Stenman (13)	glibenclamide 15 mg daily	15 insulin-treated mean BMI 22.9	4 months crossover	I+P: HbA1 9.2 ->9.1, I+G: HbA1 9.2 ->8.3[a] 25% reduction in daily insulin dose; increase[a] basal & glucagon-stimulated C-peptide; with glibenclamide lower HDL-cholesterol!
Iavicoli (38)	various drugs and doses	155 secondary failures to SU	6 months uncontrolled	FBG 12.9 ± 2.2 → 7.8 ± 2.0 (in the non-obese) FBG 13.0 ± 2.6→ 7.7 ± 1.8 (in the obese) comparable decrease in HbA1; increase in plasma C-peptide levels
Simpson (39)	glipizide 20 mg daily	20 insulin-treated mean BMI 25.5	8 weeks parallel	I+G: FBG 10.6 → 9.0, I+P: 10.4 → 10.3 HbA1 10.6 → 12.0 12.7 → 11.0 G increased insulin-mediated disposal, decreased HDL-C
Reaven (40)	glipizide 15-40 mg	18 insulin-treated mean BMI 30.9	4-6 months uncontrolled	FBG 13.0 ± 0.6 → 9.7 ± 0.7, HbA1 11.8 ± 0.6 → 10.1 ± 0.5 groups of fair and good responders, not discernable by age, sex, BMI, diabetes duration.

All studies are double-blind placebo-controlled, unless stated otherwise. BMI=body mass index (kg/m^2); IBW=% of ideal body weight; FBG=fasting blood glucose (mmol/l); BGP=24-hour blood glucose profile (mmol/l); HbA1=glycosylated haemoglobin (%); mo.=months; SU=sulphonylurea; G=glibenclamide/glipizide/gliclazide; P=placebo; I+G=insulin+glibenclamide/glipizide/gliclazide; I+P=insulin+placebo; [a] $p<0.05$; [b] $p<0.01$

Table 6. Estimated costs of insulin and combined insulin-sulphonylurea therapy in patients with type 2 diabetes mellitus, when 2 daily injections are given with use of an insulin-pen.

	Insulin alone	Insulin + sulphonylurea
Number of insulin injections	2	1 or 2
Amount of insulin (U/day)	42	26
Costs of: insulin	dfl. 2.22	dfl. 1.37
needles	dfl. 0.58	dfl. 0.38
glibenclamide 15 mg daily	dfl. 0.00	dfl. 1.66
Total costs	dfl. 2.80	dfl. 3.41

Table 7. A practical approach to combined insulin-sulphonylurea therapy in patients with type 2 diabetes.

A Patients with failure to oral hypoglycaemic agents.

1. Conversion to insulin therapy only (once or twice daily, long- or intermediate-acting +/- fast-acting)
   or:
2. Addition of low dose insulin to existing sulphonylurea-therapy:
   a. NPH- or Lente insulin before breakfast (ref. 33)
      - start with 4-8 U
      - adjust dose on basis of glucose profile
      - give two injections when insulin dose >28 U

   or:

   b. NPH- or Lente insulin at bedtime (ref. 32)
      - start with 4-8 U
      - adjust dose on basis of fasting blood glucose
      - add second injection before breakfast, when insulin dose >40 U or marked post-prandial hyperglycaemia persists

B. Insulin-treated type 2 diabetic patients.

1. If poorly-controlled, add glibenclamide (5 mg. twice daily) to improve blood glucose control.

tion was achieved, whereas marked postprandial hyperglycaemia necessitated the institution of a second (pre-breakfast) insulin injection in the others. Also in the present study, one-thirds of the patients starting with bedtime injections needed an additional morning injection of insulin. It therefore still needs to be determined which patients have the most benefit of this treatment regimen. Disadvantages may be the higher costs of combined therapy. Table 6 gives an estimate of the costs of treatment of the individual patient, as derived from the use of insulin and glibenclamide in our study. The possible positive effects on lipoprotein metabolism will be further explored during the continuation of this study.

In conclusion, the combined insulin-sulphonylurea therapy in patients with type 2 diabetes mellitus may have the following advantages:

1. lower insulin requirement.
2. improved and more stable blood glucose control.
3. in some patients necessity of only one insulin injection.
4. less hyperinsulinaemia, and therefore possibly a lower risk for the progression of atherosclerosis.
5. by promoting insulin secretion a higher concentration of insulin is present 'intraportally'.

For use in daily clinical practice, some of the approaches have been summarized in table 7 and figure 2.

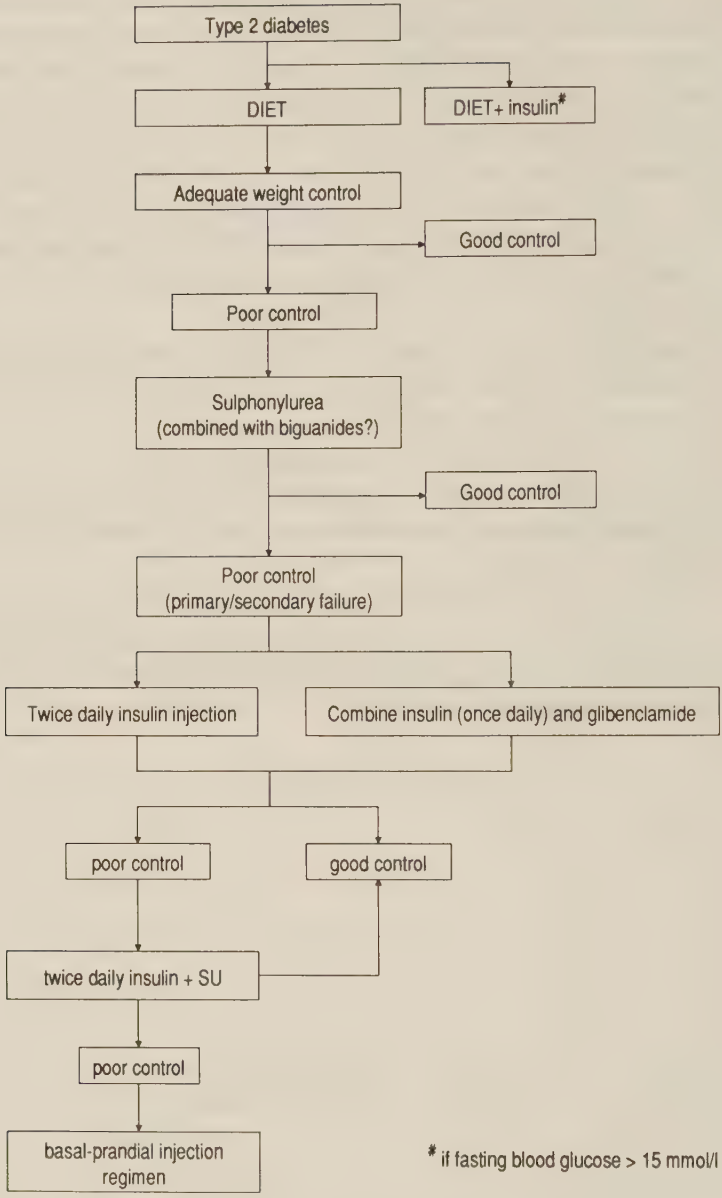

Figure 2. Schematic representation of therapy management in type 2 diabetes. Diet is the basis of treatment. In case of inadequate control (defined on an individualized approach) subsequent interventions comprise sulphonylurea, and combined therapy of insulin with sulphonylurea, or insulin alone.

REFERENCES

1. Skyler JS. Non-insulin-dependent diabetes mellitus: a clinical strategy. Diabetes Care 1984; 7 (suppl. 1): 118-129.
2. Gerich JE. Drug therapy-oral hypoglycemic agents. New Engl J Med 1989; 321: 1231-1245.
3. Wolffenbuttel BHR, Weber RFA, Koetsveld PM van, Verschoor L. Limitations of diet therapy in non-insulin dependent diabetes mellitus. Int J Obesity 1989; 13: 173-182.
4. Heine RJ. Insulin treatment of non-insulin-dependent diabetes mellitus. In: Baillière's Clinical Endocrinology and Metabolism, Non-insulin-dependent diabetes. Nattrass M, Hale PJ, Eds. London, 1988.
5. Tattersall RB, Scott AR. When to use insulin in the maturity onset diabetic. Postgrad Med J 1987; 63: 859-864.
6. Kolterman OG, Olefsky JM. The impact of sulfonylurea treatment upon the mechanisms responsible for the insulin resistance in type II diabetes. Diabetes Care 1984; 7, suppl.1: 81-88.
7. Garvey WT, Olefsky JM, Griffin J, Hamman RF, Kolterman OG. The effect of insulin treatment on insulin secretion and insulin action in type II diabetes mellitus. Diabetes 1985; 34: 222-234.
8. Montgomery BJ. High plasma insulin level a prime risk factor for heart disease. JAMA 1979; 241: 1665.
9. Stout RW. The role of insulin in atherosclerosis in diabetics and nondiabetics. Diabetes 1981; 30 (suppl 2): 54-57.
10. Nilsson A, Tideholm B, Kalen J, Katzman P. Incidence of severe hypoglycemia and its causes in insulin-treated diabetics. Acta Med Scand 1988; 224: 257-262.
11. Wolffenbuttel BHR. Combined use of insulin and oral hypoglycaemic agents in the treatment of patients with diabetes mellitus. Eur J Intern Med 1989; 1: 89-95.
12. Riddle MC, Hart JS, Bouma DJ, Phillipson BE, Youker G. Efficacy of bedtime NPH insulin with daytime sulfonylurea for subpopulation of type II diabetic subjects. Diabetes Care 1989; 12: 623-629.
13. Stenman S, Groop PH, Saloranta C, Totterman KJ, Fyhrqvist F, Groop L. Effects of the combination of insulin and glibenclamide in type 2 (non-insulin-dependent) diabetic patients with secondary failure to oral hypoglycaemic agents. Diabetologia 1988; 31: 206-213.
14. WHO Expert Committee on Diabetes Mellitus. Technical Report Series 727, 1985. Geneva: World Health Organization.
15. Johnson RN, Metcalf PA, Baker JR. Fructosamine: a new approach to the estimation of serum glycosylprotein. An index of diabetic control. Clin Chim Acta 1982; 127: 87-95.
16. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and b-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-419.
17. Bagdade JD, Buchanan WE, Kuusi T, Taskinen M-R. Persistent abnormalities in lipoprotein composition in noninsulin-dependent diabetes after intensive insulin therapy. Arteriosclerosis 1990; 10: 232-239.

18. Lindstrom T, Arnqvist HJ, Olsson AG. Effect of different insulin regimens on plasma lipoprotein and apolipoprotein concentrations in patients with non-insulin-dependent diabetes mellitus. Atherosclerosis 1990; 81: 137-144.
19. Thoelke H, Ratzmann KP. Häufigkeit des Sekundärversagens einer Sulfonylharnstofftherapie Epidemiologische Untersuchung. Dtsch Med Wschr 1989; 114: 580-583.
20. Groop LC, Pelkonen R, Koskimies S, Bottazzo GF, Doniach D. Secondary failure to treatment with oral antidiabetic agents in non-insulin-dependent diabetes. Diabetes Care 1986; 9: 129-133.
21. Ginsberg H, Rayfield EJ. Effect of insulin therapy on insulin resistance in type II diabetic subjects-evidence for heterogeneity. Diabetes 1981; 30: 739-745.
22. Wolffenbuttel BHR, Weber RFA, Van Koetsveld PM, Weeks L, Verschoor L. A randomized crossover study of sulphonylurea and insulin treatment in patients with type 2 diabetes poorly controlled on dietary therapy. Diabetic Medicine 1989; 6: 520-525.
23. Lazarus SS, Volk BB. Physiological basis of the effectiveness of combined insulin-tolbutamide therapy in stabile diabetes. Ann N Y Acad Sci 1959; 82: 590-602.
24. Jackson WPU. Sulfonylureas in the management of human diabetes. In: Campbell GD. (ed). Oral hypoglycemic agents, pharmacology and therapeutics. Acad Press, New York, p. 135-192.
25. Feinstein AR. The persistent clinical failures and fallacies of the UGDP study. Clin Pharmacol Therap 1976; 19: 78-93.
26. Kolata GB. Controversy over study of diabetes drugs continues for nearly a decade. Science 1979; 203: 986-990.
27. Hamelbeck H, Klein W, Zoltobrocki M, Schoffling K. Glibenclamide-insulin combination in the management of secondary failure of sulfonylurea medication. Dtsch Med Wschr 1982; 107: 1581-1583.
28. Groop L, Harno K, Tolppanen EM. The combination of insulin and sulphonylurea in the treatment of secondary drug failure in patients with type II diabetes. Acta Endocrinol 1984; 106: 97-101.
29. Osei K, O'Dorisio TM, Falko JM. Concomitant insulin and sulfonylurea therapy in patients with type II diabetes: effects on glucoregulation and lipid metabolism. Am J Med 1984; 77: 1002-1009.
30. Groop L, Harno K, Nikkila EA, Pelkonen R, Tolppanen EM. Transient effect of the combination of insulin and sulfonylurea (glibenclamide) on glycemic control in non-insulin-dependent diabetics poorly controlled with insulin alone. Acta Med Scand 1985; 217: 33-39.
31. Lardinois CK, Liu GC, Reaven GM. Glyburide in non-insulin-dependent diabetes: its therapeutic effect in patients with disease poorly controlled by insulin alone. Arch Intern Med 1985; 145: 1028-1032.
32. Quatraro A, Consoli G, Ceriello A, Giugliano D. Combined insulin and sulfonylurea therapy in non-insulin-dependent diabetics with secondary failure to oral drugs: a one year follow-up. Diabete & Metabolisme 1986; 12: 315-318.
33. Longnecker MP, Elsenhans VD, Leiman SM, Owen OE, Boden G. Insulin and a sulfonylurea agent in non-insulin-dependent diabetes mellitus. Arch Intern Med 1986; 146: 673-676.

34. Simonson DC, Delprato S, Castellino P, Groop L, DeFronzo RA. Effect of glyburide on glycaemic control, insulin requirement, and glucose metabolism in insulin-treated diabetic patients. Diabetes 1987; 36: 136-146.
35. Gutniak M, Karlander SG, Efendic S. Glyburide decreases insulin requirements, increases beta-cell response to mixed meal, and does not affect insulin sensitivity: effects of short- and long-term combined treatment in secondary failure to sulfonylurea. Diabetes Care 1987; 10: 545-554.
36. Castillo M, Scheen AJ, Paolisso G, Lefebvre PJ. The addition of glipizide to insulin therapy in type II diabetic patients with secondary failure to sulfonylureas is useful only in the presence of a significant residual insulin secretion. Acta Endocrinol 1987; 116: 364-372.
37. Schade DS, Mitchell WJ, Griego G. Addition of sulfonylurea to insulin treatment in poorly controlled type II diabetes a double-blind, randomized clinical trial. JAMA 1987; 257: 2441-2445.
38. Iavicoli M, Cucinotta D, De Mattia G, *et al.* Blood glucose control and insulin secretion improved with combined therapy in type 2 diabetic patients with secondary failure to oral hypoglycaemic agents. Diabetic Med 1988; 5: 849-855.
39. Simpson HCR, Sturley R, Stirling CA, Reckless JPD. Combination of insulin with glipizide increases peripheral glucose disposal in secondary failure type 2 diabetic patients. Diabetic Med 1990; 7: 143-147.
40. Reaven GM, Fraze E, Chen NY, Hollenbeck C, Chen Y-DI. The combined use of insulin and sulfonylurea therapy in patients with non-insulin dependent diabetes mellitus. Horm Metabol Res 1989; 21: 132-136.
41. Riddle MC. Evening insulin strategy. Diabetes Care 1990; 13: 676-686.
42. Riddle MC, Hart JS. Which patients might benefit from combining a sulfonylurea with insulin? (letter) Diabetes Care 1985; 8: 205-205.
43. Taskinen MR, Sane T, Helve E, Karonen SL, Nikkila EA, Yki-Jarvinen H. Bedtime insulin for suppression of overnight free-fatty acid, blood glucose, and glucose production in NIDDM. Diabetes 1989; 38: 580-588.

CHAPTER 9

Determinants of the behaviour 'injecting insulin' in elderly patients with diabetes mellitus

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Submitted

SUMMARY

In patients with type 2 diabetes mellitus blood glucose control may gradually worsen despite diet and oral hypoglycaemic agents. We investigated which possible factors determine the decision for elderly type 2 diabetic patients to start with insulin therapy in this situation. According to Fishbein and Ajzen a attitude-behaviour model was constructed which included the determinants intention, attitude, subjective norm and self-efficacy. Fifty-three patients (age 68 ± 9 years) participated in the study: 26 already used insulin for 7 (1-12) months, 27 were tablet-treated but poorly-controlled (fasting blood glucose >8.0 mmol/l and glycosylated haemoglobin >8.0%). A high correlation ($r=0.81$, $p<0.001$) existed between the intention to and the actual use of insulin therapy. The main factor (70%) explaining the intention towards insulin treatment was the subjective norm: patients are guided by the opinion of important other persons, especially the treating internist, the family physician and the diabetes nurse. Tablet-treated patients reported a negative opinion of their physician towards their treatment with insulin. Intention to behaviour was also determined by self-efficacy, e.g. expectations about the skills concerning injecting insulin. Self-monitoring of blood glucose and knowledge about diabetes positively influenced self-efficacy, attitude towards and intention to use insulin. Education needs to enforce the subjective norm and improve the patient's self-efficacy. A stimulating attitude of the treating physician towards insulin therapy is essential.

INTRODUCTION

In patients with type 2 diabetes mellitus, insulin therapy may be needed, when diet and oral hypoglycaemic agents can no longer adequately control diabetes (1). Many patients with this so-called secondary failure are not motivated to switch to insulin injections. Several reasons are given for this reluctance: at first, patients often do not perceive complaints, not even in the presence of severe hyperglycaemia, and therefore do not think that insulin treatment will improve their well-being (2). Secondly, lack of knowledge concerning the relation between high blood glucose levels and the occurrence of secondary diabetic complications (3,4) might influence the beliefs about insulin treatment. Thirdly, the perceived disadvantages of insulin therapy may outweigh in the patient's point of view the possible beneficial effects, and the patient may even be convinced that he or she is not capable to perform the difficult actions of injecting insulin. These views are often reinforced when a physician is reluctant -for whatever reason- to switch elderly patients to insulin therapy.

Despite this, a growing number of elderly type 2 diabetic patients is at present being treated with insulin. The use of insulin pens (5) makes the start of this treatment more easily. The present study was undertaken in order to evaluate which factors determine the decision of diabetic patients failing on oral therapy to accept to use insulin and whether these factors have to be the goal for specific education.

PATIENTS AND METHODS

Patients

Patients with type 2 diabetes (6), who were regularly seen by an internist/diabetologist at the outpatient-clinic of the Department of Internal Medicine, were elegible for the study, when they no longer responded to oral hypoglycaemic agents (tablet-group), or had started insulin therapy for this reason during the previous year (insulin-group). Failure to respond to oral therapy was defined as presence of fasting blood glucose levels >8.0 mmol/l, and glycosylated haemoglobin (HbA_{1c}) >8.0% with maximal doses of sulphonylurea. During a period of two months 56 consecutive patients were thus selected. Three patients refused to participate. Of the 53 remaining patients, 23 were men and 30 women, with a mean age ($\pm$ SD) of 68 $\pm$ 9 years. Twenty-six of them were using insulin. They were all treated by the same internists. Patients were interviewed by the same investigator (CHCD). Interviews took place at the outpatient-clinic

just before the visit to the diabetologist, or at the patient's home at least two weeks after the last visit to the clinic. With 22 of the 27 tablet-users the advantages and drawbacks of insulin treatment was already discussed at -at least- one occasion.

Design of the behaviour model

For the analysis we used the theoretical model of Fishbein and Ajzen (7,8). This 'theory of reasoned action' regards human behaviour as a rational one. In general, man considers the implications of his actions before he decides to engage or not to engage in a certain behaviour. Thus, a person's intention to (or not to) perform is the immediate determinant of the behaviour. Two basic determinants directly influence a person's intention: his attitude and the subjective norm. A person's attitude is the result of a balance between perceived advantages and disadvantages of a certain behaviour. Attitude is composed of two elements: several relevant beliefs, described as the expectations which outcome a certain behaviour will yield, and the evaluation of these beliefs. The subjective norm describes the influence of specific individuals or groups on the behaviour of a person. The subjective norm consists of two elements: normative beliefs, which are the perceived expectations of specific reference persons, for instance the mother, an other relative, or the physician, and the motivation to comply, which depicts whether the opinion of other persons indeed influences or changes intention. Examples of these determinants are given in table 1. In addition, the concept of self-efficacy (9,10) has been implemented in the model. Although the patient may be convinced that insulin treatment is desirable, he/she may consider himself incapable to perform the behaviour and therefore have a negative intention towards insulin treatment. Self-efficacy comprises the expectations of a person that he will be able to perform the behaviour injecting insulin. Furthermore, we included those external variables, which are likely to be related to and of importance for the behaviour of injecting insulin, such as well-being, mode of treatment, and knowledge of diabetes (11).

The questionnaire

In a pilot study, 11 other type 2 diabetic patients were interviewed about aspects of insulin therapy to elicit the most important salient beliefs and normative beliefs. Six of these patients were treated with insulin, and five were 'secondary failures' to sulphonylureas.

Table 1. Aspects of the Fishbein and Ajzen model.

Behaviour:	'starting insulin therapy'
Intention:	'do you intend to start or continue insulin therapy during the next 6 months?'
Belief:	'when I will inject insulin this will take a lot of time'
	'when I will inject insulin I will feel better'
Evaluation of this belief:	'spending a lot of time on my diabetes treatment does not bother me at all / does bother me very much'
Normative belief:	'my doctor thinks that I should be put on insulin'
Motivation to comply:	'when it comes to injecting insulin, the opinion of my doctor is not/very important'

Attitude was measured with 14 thus-derived questions relating to both positive and negative consequences of injecting insulin. These consequences were evaluated on a +2 (very good) to -2 (very bad) scale. For each belief (b), the patients were asked to indicate the likelihood of certain consequences with a score from 0 (very unlikely) to +3 (very likely). A person's attitude was calculated by summation of the products of evaluation and likelihood of all 14 consequences. Summation yielded a reliable measure (Cronbach's alpha (12) 0.67).

Subjective norm was measured with 8 questions concerning important reference persons (partner, children, family physician, internist, diabetes nurse). Patients were asked to indicate the perceived opinion of these reference persons (normative belief) and how much they cared about these opinions (motivation to comply). By summating the products of normative beliefs and motivation to comply a person's subjective norm was calculated. Reliability testing proved that, after elimination of one item, this subjective norm scale was a reliable measure (Cronbach's alpha 0.74).

Self-efficacy was measured with 7 questions on technical aspects of administering insulin by injection. Respondents were asked to indicate in which degree they regard themselves capable to perform each aspect of the behaviour. The scores ranged from -2 (absolutely incapable) to +2 (absolutely capable). In addition, the behaviour injecting insulin was placed in three daily-life situations. Respondents were asked to indicate how capable they regarded them-

selves to perform the behaviour in each situation, and further to indicate how often each situation would occur to them. Summation of the questions yielded a reliable measure (alpha coefficient 0.84).

The intention to behaviour was assessed by asking whether the patient intended to use or continue the use of insulin therapy during the next 6 months. Scores ranged from +2 (yes, certainly) to -2 (definitely not).

The physical variables recorded are body weight, blood glucose control, self-monitoring of blood glucose. On a 0-3 scale respondents could indicate how frequent a certain complaint or symptom due to the presence of hyperglycaemia or due to specific diabetic complications had occurred during the preceeding 4 weeks. The combination of the answers to these 18 questions yielded a Symptom Score (Cronbach's alpha 0.85).

Treatment variables comprised the actual therapy and the number of occasions during which insulin therapy was discussed between the physician and the patient. Personal variables included age, sex, marital and social status. The latter represented previous education, profession, and profession of the spouse. Twenty multiple-choice questions covering various aspects of diabetes were prepared in our clinic (alpha coefficient 0.77).

Laboratory determinations

Fasting blood glucose was measured in venous whole blood with an automated hexokinase method. HbA_{1c} was determined with HPLC (DIAMAT, Bio-Rad Laboratories, Richmond, Ca., USA). Normal values are 4.4-6.2%, mean 5.3%, between-assay cv 2.6%.

Statistical analyses

All data are expressed as mean ± SD. Differences between group means were tested with unpaired Student's t test or non-parametric test when appropriate. Corrections for multiple comparisons were made. Variables were compared by Pearson's correlation coefficient based on least-squares regression analysis. The predictive value of attitude, subjective norm, self-efficacy and the external variables for intention was determined stepwise with intention as dependent variable. External variables were only entered if they had a significant linear correlation with intention. The same procedure was performed for behaviour.

RESULTS

Diabetes and its therapy

Six of the 26 patients on insulin took one daily injection, all in combination with sulphonylurea, 19 patients took two injections, whereas 1 was on a 4-injection regimen. Eleven of the 27 tablet-treated patients included in the study used sulphonylurea only, and 16 used both sulphonylurea and metformin. Known duration of diabetes was 8 (range 1-23) years in the patients on insulin, and 12 (range 1-30) years in the tablet-treated patients. Duration (± SD) of insulin therapy was 7 ± 3 months, daily insulin dose was 36 ± 13 U. Their fasting blood glucose was 9.1 ± 3.5 mmol/l, and HbA_{1c} 8.5 ± 1.9%. Before the start of insulin therapy these values were 16.7 ± 4.1 mmol/l and 11.3 ± 1.8%, respectively (both $p<0.001$ compared to values during insulin). Fasting blood glucose of the tablet-treated patients was 11.7 ± 3.6 mmol/l, and HbA_{1c} 9.3 ± 1.7% (both $p<0.05$ compared to insulin-group). Seventeen patients on insulin and 10 tablet-users were regularly performing self-monitoring of blood glucose. Retinopathy was present in 20%, and microalbuminuria or proteinuria was established in 45% of the patients.

Attitude, subjective norm and self-efficacy

Of all patients 10 had a negative attitude, and 41 a positive attitude towards injecting insulin. The scores on the determinants of the model is given in table 2. Attitude score, subjective norm and self-efficacy were higher in insulin-treated patients.

The relations between the different components of the model is shown in figure 1. Intention and behaviour were strongly correlated, indicating that patients stating a positive intention towards insulin treatment really would perform the behaviour. The strongest relation was found between subjective norm and intention ($r=0.83$, $p<0.001$). Attitude and self-efficacy showed a significant, but less strong relation with intention. The intention explained for 66% the behaviour. Stepwise regression revealed that 70% of this intention could be explained by the subjective norm, and an additional 5% by self-efficacy. Attitude yielded no significant additional explanation for the observed intention.

Table 3 gives an overview of the scores of insulin- and tablet-users regarding the various beliefs on insulin treatment. Tablet-users reported less positive expectations of benefit from insulin therapy. Both for insulin- and tablet-users the strongest reference persons are the treating internist, the diabetes nurse and

Table 2a. Average scores on determinants of the attitude-behaviour model in type 2 diabetic patients on insulin (n=26) and patients using oral hypoglycaemic agents (n=27).

	Insulin	Tablets
Intention	1.9	-0.9 #
Attitude	18.4	4.4 #
Subjective norm	16.5	0.4 #
Self-efficacy	21.4	7.8 #

# $p<0.01$ compared to insulin-group

Table 2b. Average scores on determinants of the attitude-behaviour model in type 2 diabetic patients starting insulin within one month after the interview (n=5) and patients continuing the use of oral hypoglycaemic agents (n=22).

	Starting insulin	Continuing tablets
Intention	1.0	-1.4 #
Attitude	14.4	-7.8 *
Subjective norm	16.8	-5.8 #
Self-efficacy	16.0	1.8 *

* $p<0.05$, # $p<0.01$ compared to patients starting insulin

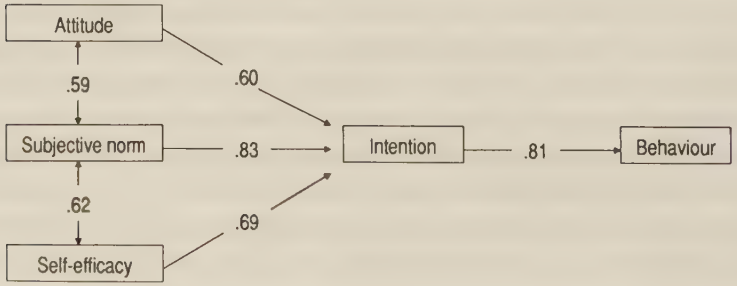

Figure 1. Individual correlations between the determinants of the behaviour 'injecting insulin'; all correlations are significant at the $p<0.01$ level.

Table 3. Mean scores of insulin and tablet-users on beliefs (b), evaluations (e) and their product (b x e) concerning injecting insulin.

consequence	beliefs		evaluations		b x e	
	insulin	tablets	insulin	tablets	insulin	tablets
When I inject / would inject insulin:						
- my bloodsugars will decrease	2.96	2.19*	1.27	1.96*	3.85	4.26
- the chance to get complications will decrease	2.54	1.37*	1.96	1.85	4.96	2.48*
- I will feel better	2.42	1.07*	1.96	1.93	4.77	2.15*
- the injection will hurt	0.50	1.30	-1.42	-1.48	-0.92	-2.22
- other people will notice that I have diabetes	0.46	0.96	-0.69	-1.11	-0.46	-1.22
- I would have to adhere to strict times	1.73	2.63*	-0.58	-1.30	-1.08	-3.15
- It will cost me lots of time	0.00	0.74*	-0.85	-1.00	0.00	-0.74*
- I will have to stay at home more	0.08	1.19*	-1.19	-1.48	0.00	-1.44*
- I will have to adhere more strictly to my diet	1.42	1.22	-1.50	-1.48	-1.96	-1.92
- I will have less thirst	2.00	0.96*	0.88	0.56	1.96	0.52
- I will have to void less	1.46	1.15	1.08	0.93	1.42	1.11
- I will feel less tired	1.31	1.07	1.92	1.78	2.62	2.15
- I will feel less tense	1.04	0.78	1.69	1.48	1.62	1.48
- I will experience less itch	1.19	0.56	0.88	0.85	1.65	0.96

* $p<0.05$ compared to insulin-group;

Ranges of score: beliefs: score 0 (very unlikely) to 3 (very likely); evaluations: score -2 (very negative) to +2 (very positive); b x e: score -6 to + 6 (products)

the family physician (m.c. score 2.15-3.00, table 4). Relatives are only weakly motivating persons. Tablet-users reported a slightly negative opinion of their treating physician towards their using insulin, and a low score on their expectation to be capable to inject insulin (table 5).

Within one month after the interview, 5 tablet-treated patients started to use insulin. Their scores on intention, attitude, subjective norm and self-efficacy were significantly more positive than in the remaining patients of the tablet-group (table 2b), and not different from the patients who already used insulin.

Table 4. Mean scores of insulin and tablet-users on normative beliefs (n.b.), motivation to comply (m.c.) and their product (n.b. x m.c.) concerning injecting insulin.

persons	normative beliefs		motivation to comply		n.b. x m.c.	
	insulin	tablets	insulin	tablets	insulin	tablets
partner	1.35	-0.59*	0.62	0.96	1.23	-0.41
children	1.38	0.07*	0.46	0.63	0.92	0.44
friends	0.19	0.04	0.19	0.22	0.08	0.07
other diabetic patients	0.42	0.07	0.50	0.93	0.46	0.37
family physician	1.31	-0.26*	2.15	2.44	3.38	-0.37*
internist	2.00	-0.04*	3.00	2.85	6.00	-0.15*
diabetes nurse	1.54	0.11*	2.19	1.22	4.38	0.44*

* $p<0.05$ compared to insulin-group; Range of scores: normative beliefs: score -2 (very negative) to +2 (very positive); motivation to comply: score 0 (not important) to +3 (very important); n.b. x m.c.: score -6 to + 6 (products)

Table 5. Mean scores of insulin and tablet-users on items of self-efficacy.

	insulin	tablets
Do you think that you are or will be capable to (a):		
- puncture yourself	1.73	0.22 #
- inject your insulin	1.73	-0.33 #
- learn to inject insulin	1.85	0.59 #
- start with insulin therapy, when someone else will administer it	1.31	0.78
- have your syringe or insulin pen always available	2.00	1.15 #
- can watch the moments that you need to inject insulin	2.00	1.30 #
- inject the correct amount of units	1.77	0.07 #
Frequency of daily-life situations, and estimated capability to inject insulin in the circumstances (b):		
- when you are on holidays	2.44	1.08
- when you are out visiting friends	3.52	1.00 #
- when you are out eating in a restaurant	2.26	0.62*

* $p<0.05$; # $p<0.01$ compared to insulin-group;
Range of scores: (a). -2 (absolutely not) to +2 (absolutely yes);
(b). -6 (absolutely not) to +6 (absolutely yes)

External variables

Insulin-treated patients gave more correct answers on the 20 questions concerning diabetes knowledge than tablet-treated (13.0 *vs.* 10.2, p=0.011). However, when the three questions related to insulin therapy were omitted from the analysis, the difference no longer existed. A good correlation was found between knowledge and level of education (r=0.47, p<0.01). The calculated Symptom Score was not different between insulin and tablet-users (p=0.209). No single symptom occurred more in one of the groups. Thirty-five patients found themselves rather or very healthy, whereas 6 patients reported themselves as rather or very ill. No correlation was found between the determinants of the model and external variables as sex, age, educational and social status, duration of diabetes, perceived hyperglycaemic symptoms, blood glucose control and presence of secondary complications. However, a positive correlation existed between attitude and knowledge of diabetes (r=0.50, p<0.01), and between attitude and the fact whether self-monitoring of blood glucose was performed (r=0.32, p<0.05). Both variables were also strongly correlated with self-efficacy (r=0.52 and r=0.46, respectively, both p<0.01).

DISCUSSION

This study is to our knowledge the first to report which factors determine the willingness of elderly type 2 diabetic patients, who are poorly controlled on tablets, to use insulin therapy. Various models have been employed to provide a better understanding of self-care behaviour of patients with diabetes mellitus. The widely-used Health Belief model (13,14) has some drawbacks related to lack of uniformity of used definitions, the fact that influences of the social environment are considered of minor importance (15), and the lack of reliable and valid diabetes-specific measures (16). To study the behaviour 'injecting insulin' we used the Fishbein and Ajzen attitude-behaviour model. In this theory, the relation between the determinants attitude, subjective norm, and self-efficacy and the intention to perform a certain behaviour is described. The validity of the model has been proved several times for diabetes-related (17-19) and other kinds of health behaviour (20), and the derived information can be directly used for the development and subsequent evaluation of diabetes education programs (15). Other factors, such as level of knowledge, demographic variables and health locus of control (21,22) are considered prerequisites in this model, and are incorporated as the 'external variables'. In our patients we found a high correlation (r=0.81, p<0.001) between the intention to and the desired

behaviour 'injecting insulin'. Persons with a positive intention were very likely to adopt the behaviour. This was found in **retrospect**, in the patients who already used insulin, and in addition also **prospectively** in those tablet-treated patients, who started insulin within one month after the interview. The subjective norm was the most important factor to explain the measured intention to commence insulin therapy. This implies that patients are guided in their willingness to accept insulin treatment by the opinion of important other persons. Especially the judgement of the treating internist and -to a lesser extent- the family physician and the diabetes nurse was regarded as very important in this respect. The opinion of relatives was less important in this respect. In contrast, tablet-treated patients reported a slightly negative opinion of their treating physician towards insulin therapy. In a study on diet compliance of diabetic patients the social norm was also found to be the strongest predictor of behavioural intention (17).

Intention was also determined by the factor self-efficacy. This determinant summarizes several skills related to the technique of injecting insulin. It appears that in particular patients who regard themselves capable to perform the behaviour 'injecting insulin' will progress to a positive intention. Learning to actually administer the injection, and establishing the correct amount of insulin are especially reported as difficult. It must be stressed that the type 2 diabetic patients studied are treated by endocrinologists at the outpatient clinic of a teaching hospital. A considerable number of them has been referred by their general practitioner for evaluation and treatment of their diabetes. In some instances, the possible institution of insulin therapy was the reason for referral; this was discussed with the patients on one or more occasions.

Fishbein and Ajzen state in their model that demographic variables and personality treats only have an indirect influence on the behaviour of a person through the attitude and the subjective norm. For practical purposes these variables are of importance, since they may form a direct entrance for education. It can be expected that patients with poor control who experience complaints will have a more positive attitude towards insulin therapy. The presence of secondary complications, or fear for these to develop may enhance the intention to start with insulin therapy in an earlier phase, although this will mainly occur when a physician has introduced this possibility of treatment. However, this factor may also have a negative influence: a patient can -for instance- regard himself uncapable to inject insulin because of poor vision, thereby lowering the intention. Further, lack of knowledge about diabetes and insulin therapy will lead to a more negative attitude. We found no correlation between perceived symptoms and intention, neither was any relation demonstrable between intention and several external variables, such as age, sex,

education, social status, presence of eye complications, or duration of disease. However, patients with better knowledge of diabetes or performing self-monitoring of blood glucose showed a more positive attitude and intention. Thus, enforcing these external factors by education may positively influence intention towards insulin therapy. The high number of our patients already performing self-monitoring of blood glucose (51%) is explained by our early use of this technique in diabetes education programs, monitoring progress during dietary therapy, and to prepare them for the conversion to insulin treatment.

The negative opinion on insulin therapy that tablet-users derive from their physician is not easily explained. All patients are treated by the same internists. With 22 of the 27 tablet-users the advantages and drawbacks of insulin treatment was already discussed at -at least- one occasion. A higher subjective norm was found among the patients, with whom insulin therapy had been discussed at repeated visits, and who subsequently started with insulin. This suggests that the subjective norm is built gradually with repeated discussions. Thus, several patient visits or educational sessions are needed to establish a stronger social norm and a more positive attitude towards insulin therapy. It can, however, not be ruled out that the low intention to behaviour and attitude of tablet-users is due to a poor perception of the given information. Another factor may be that their blood glucose control was less deranged than in the insulin-treated patients before this group started on insulin; the advice of the internist to start insulin therapy may be put to them less strongly.

We conclude that the Fishbein and Ajzen model is very useful to explain the behaviour 'injecting insulin'. For the willingness of type 2 diabetic patients to use insulin the opinion of other important persons, especially the internist/diabetologist, the family physician and the diabetes nurse, appeared the most significant factor. The patient's estimate to be able to perform the technique of injecting insulin adequately was a second major determinant. This implies that education of patients, in case such a change of therapy is advised, must aim to enforce the subjective norm and improve self-efficacy. Improving diabetes knowledge and stimulating self-monitoring of blood glucose may promote self-efficacy and thereby the intention to commence insulin therapy. A positive attitude of the treating physician towards insulin therapy is essential.

REFERENCES

1. Tattersall RB, Scott AR. When to use insulin in the maturity onset diabetic. Postgrad Med J 1987; 63: 859-864.
2. Tattersall RB. Diabetes in the elderly; a neglected area? Diabetologia 1974; 27: 167-173.

3. The DCCT Research Group: Diabetes Control and Complications Trial (DCCT): design and methodological considerations for the feasibility phase. Diabetes 1986; 35: 530-545.
4. Tchobroutski G. Relation of diabetic control to development of microvascular complications. Diabetologia 1978; 15: 143-152.
5. Berger AS, Saurbrey N, Kuhl C, Villumsen J. Clinical experience with a new device that will simplify insulin injections. Diabetes Care 1985; 8: 73-76.
6. WHO Expert Committee on Diabetes Mellitus. Technical Report Series 727, 1985. Geneva: World Health Organization.
7. Fishbein M, Ajzen I. Belief, attitude, intention and behaviour; an introduction to theory and research. Reading, MS, Addison Wesley, 1975.
8. Ajzen I, Fishbein M. Understanding attitudes and predicting social behaviour. Englewood Cliffs, NJ, Prentice Hall, 1986.
9. Bandura A. Social Foundations of Thought and Action: A Social Cognitive Theory. Englewood Cliffs, NJ, Prentice Hall, 1986.
10. Strecher VJ, McEvoy De Vellis B, Becker MH, Rosenstock IM. The role of self-efficacy in achieving health behaviour change. Health Educ Q 1986; 13: 73-91.
11. Jacobsen AM, Hauser ST. Behavioural and psychological aspects of diabetes. In Diabetes mellitus: Theory and Practice. 3rd Ed. Ellenberg M, Rifkin H, Eds., Elsevier Science Publishing Co, New Hyde Park, NY, 1990.
12. Cronbach LJ, Meehl PE. Construct validity in psychological tests. Psych Bull 1955; 4: 281-302.
13. Rosenstock IM. Understanding and enhancing patient compliance with diabetic regimens. Diabetes Care 1985; 8: 610-616.
14. Anderson LA. Health-care communication and selected psychosocial correlates of adherence in diabetes management. Diabetes Care 1990; 13 (suppl. 2): 66-76.
15. Janz NK, Becker MH. The health belief model: a decade later. Health Educ Q 1984; 11: 1-47.
16. Lewis KS, Jennings AM, Ward JD, Bradley C. Health belief scales developed specifically for people with tablet-treated type 2 diabetes. Diabetic Med 1990; 7: 148-155.
17. Shenkel RJ, Rogers JP, Perfetto G, Levin RA. Importance of 'significant others' in predicting cooperation with diabetic regimen. Int J of Psychiatry in Med 1986; 15: 149-155.
18. De Weerdt I, Visser AP, Kok GJ, Van der Veen EA. Determinants of active self-care behaviour of insulin treated patients with diabetes: implications for diabetes education. Soc Sci Med 1990; 30: 605-615.
19. De Weerdt I, Visser AP, Van der Veen EA. Attitude behaviour theories and diabetes education programmes. Patient Education and Counseling 1989; 14: 3-19.
20. De Vries H, Kok GJ. From determinants of smoking behaviour to the implications for a prevention programme. Health Educ Res 1986; 1: 85-94.
21. Ruzicki DA. Relationship of participation preference and health locus of control in diabetes education. Diabetes Care 1984; 7: 372-377.
22. Schlenk EA, Hart KL. Relationship between health locus of control, health value, and social support and compliance of persons with diabetes. Diabetes Care 1984; 7: 566-574.

CHAPTER 10

General discussion

TYPE 2 DIABETES MELLITUS

Non-insulin-dependent or type 2 diabetes mellitus is a heterogeneous disorder, characterized by impaired insulin secretion by the islet B-cells, diminished peripheral insulin action, and increased hepatic glucose production (1,2). The major therapeutic goals in type 2 diabetic patients are to optimize blood glucose control, to reduce overweight and to normalize lipid disturbances and elevated blood pressure, in order to improve the well-being of the patient and reduce the risk for the development of late diabetic complications (3-5). Exercise (6) and diet, aiming at weight reduction (7-9) are the cornerstones of therapy. However, often pharmacologic treatment is necessary, in which case sulphonylurea (10), metformin or insulin may be employed (11).

DIABETIC COMPLICATIONS

Secondary complications are frequently observed in patients with type 2 diabetes mellitus. The role of diabetes as an independent risk factor for cardiovascular disease is well established (12). In patients, a two- to three-fold increase of morbidity and mortality attributed to coronary heart disease (CHD) is demonstrated (13,14). A comparable increase of peripheral vascular disease is demonstrated (15). Microvascular abnormalities can be found in a considerable number of patients. Retinopathy is observed in 12 to 44% of diabetic patients 10 years after diagnosis. Diabetic nephropathy is less frequently found in type 2 compared to type 1 diabetic patients (14).

A number of risk factors for CHD can be demonstrated in diabetic patients. Twenty to 50% of them suffer from hypertension (16). Lipid abnormalities, comprising elevations of both LDL-cholesterol and VLDL-triglycerides, as

well as decreases in the levels of HDL-cholesterol are reported to occur in at least 30% of patients (17). In diabetic patients elevated triglyceride levels seem to be an independent risk factor for the development of macrovascular disease.

In the Netherlands, only few data are available concerning the prevalence of late complications in type 2 diabetic patients (18). In comparison with patients who are under care by their family physician, a larger number of our hospital-treated patients uses insulin (48% *vs.* 22%). With this somewhat more difficult therapy, better metabolic control can be achieved. Based on epidemiologic data at least 20% of patients treated by their general practitioner show such poor metabolic control that they should be treated with insulin (18). In addition, the prevalence of vascular abnormalities in our patients was higher than that reported in the population in the general practice. This high prevalence of coronary artery disease (48%), hypertension (56%), cerebrovascular disease (15%) and peripheral artery disease (35%) implies a tendency for clustering of more complicated patients with type 2 diabetes in a hospital-clinic. This may be caused by the necessity of more aggressive treatment after a vascular problem has been diagnosed, for instance the institution of insulin therapy because of diabetic foot problems, or worsening of control after myocardial infarction. Otherwise, patients in poor control are more likely to be referred by their general practitioner for treatment advice and insulin therapy, although the criteria for good and poor control are often interpreted very liberally.

Especially in the patients with elevated urinary albumin excretion a higher prevalence of hypertension, cerebrovascular and peripheral vascular disease, neuropathy and retinopathy is found in comparison to normoalbuminuric patients, as described in chapter 2. This is in agreement with other reports (19,20). Not only the presence of macroproteinuria (urinary protein excretion $\geq$ 300 mg/24h), but already the presence of traces of albumin (microalbuminuria, albumin excretion 30-300mg/24h) are strongly associated with subsequent mortality (21,22). Therefore, determination of microalbuminuria can identify patients with high risk of acute cardiovascular events.

In diabetic patients, hypercholesterolaemia is associated with a very high risk of developing coronary heart disease and dying from cardiovascular causes in comparison to non-diabetic subjects and diabetic subjects with normal cholesterol levels (23,24). In our studies, total and LDL-cholesterol were considerably higher, and HDL-cholesterol was lower compared to non-diabetic individuals. Furthermore, although metabolic control was good in the diet-treated patients, they tended to have higher total cholesterol and triglyceride levels, and lower HDL-cholesterol compared to insulin-treated patients.

In diabetic patients, who are chronically admitted to a nursing home, a higher prevalence of cerebrovascular disease, peripheral vascular abnormalities, skin necrosis or leg ulcers and recurrent urinary tract infections can be found compared to patients treated at the hospital outpatient-clinic (25). Hypertension is found in almost 50% of all patients, whereas its prevalence is the highest in the stroke patients. In the ambulatory patients cardiac complaints are more prevalent. Use of medication, especially diuretics and anticoagulant agents, is very high, not only in the nursing home patients, but also in the ambulatory patients. Only 25% of patients do not use any medication besides their specific diabetes-therapy. Thus, diabetes and the sequelae of its macrovascular complications may greatly impair the quality of life of the diabetic patient. Ischaemic heart disease is the great killer in these patients, and especially stroke and peripheral vascular disease are risk factors for admission to a nursing home. Better identification and preventive treatment of diabetic patients with high risk of ischaemic heart disease, stroke and peripheral vascular disease is necessary. This goal can only be reached, when regular screening and follow-up appointments of patients, either by the internist/diabetologist or by the general practitioner, comprise measurement of the abovementioned relevant measures (blood pressure, HbA_{1c}, plasma lipids, microalbuminuria), and more aggressive therapeutic interventions to normalize these variables. The current recommendations of the Dutch Standard of Care for General Practitioners do not fulfil these criteria (26).

MONITORING OF METABOLIC CONTROL

The measure most frequently used to monitor metabolic control in type 2 diabetic patients is the level of fasting blood glucose. It has been advocated to rely on this measure in all patients irrespective of their treatment (diet, oral agents, insulin) (27). Some outpatient and shared-care clinics have been especially organized to measure fasting blood glucose and perform the follow-up visit of the patient on the same morning. We and others (28,29) have, however, demonstrated that the power of fasting blood glucose levels to correctly predict adequate metabolic control, as assessed by measurement of the 'Golden Standard', glycosylated haemoglobin (HbA_{1c}), with a very reliable and reproducible method, is rather poor, not only in insulin-treated patients, but also in diet- and tablet-treated patients. These findings have serious impact on the daily care for patients. On one hand, an additional measurement has to be performed, with an increase in costs, and the patient will have to visit the clinic or his doctor a few days in advance of the actual follow-up appointment to have the results availa-

ble the day of his check-up. On the other hand, by measuring HbA_{1c} a considerable number of patients will be identified who are inadequately controlled, and need intensification of therapy. This point is also relevant for patients treated by their general practitioner (30). Starting with insulin injections in an earlier phase may very well improve patients' well-being, and prevent some of the later complications, especially in the younger patients.

Other measures of glycated proteins have been used to assess short- or long-term metabolic control. One of the more popular is the measurement of glycated serum proteins, the so-called serum fructosamine determination (31,32). It has been introduced because of its presumed ease of measuring and automation of the assay, as well as its lower price. Lack of standardization is the main problem prohibiting the clinical utilization of this assay. The most frequently used commercially available kit has suffered considerable adaptations at least three times during the last five years. Further, it has become clear that serum fructosamine determinations show a considerable variation, as demonstrated in chapter 4. Various factors contribute to this variation, such as the serum albumin level, the collection of blood (venous congestion, position of the patient), ambulation, and even circadian variations, which show an increase of fructosamine levels after breakfast. Therefore, in agreement with recent publications we tend to regard the serum fructosamine assay, although cheaper and easier to perform, not to be the long-awaited successor of the HbA_{1c} assay.

DIETARY THERAPY

The effects of dietary measures has been the subject of a vast amount of studies (7-9). Diet in the diabetic patient has evolved from restriction of refined carbohydrates and careful assessment of every gram of food eaten to a more liberalized advice aiming at healthy eating habits, abolishing as much as possible (but not forbidding) refined sugars, fat, and our Western junk food. In general, results of strict dietary therapy have been rather disappointing. Weight reduction is absolutely necessary to attain and retain improvement of metabolic control. Intensified regimens including modified fasting periods during long hospital admissions have been shown to improve blood glucose control and dyslipidaemia considerably (9,33,34), but the long-term benefits of such expensive treatments have been rather poor. We assessed the effects of dietary therapy applied in the everyday setting of control of patients at the outpatient clinic. It is confirmed that in the obese patients weight reduction is essential to result in metabolic improvement. This improvement is irrespective of the preceeding fasting blood glucose concentration. Those patients with less impaired

B-cell function and shorter known duration of diabetes show the most favourable response. As in other studies, enhancement of beta-cell function and insulin action appear to be responsible for the improvement in blood glucose control. It may, however, also be interpreted that the smaller intake of carbohydrates and the resulting weight loss result in lower blood glucose levels, which in turn is responsible for the observed improvement of islet B-cell function and insulin action by reducing glucose toxicity.

INSULIN THERAPY

Despite diet, normoglycaemia is not achieved in a considerable number of patients. In such circumstances, therapy with oral hypoglycaemic agents or insulin may be warranted. The comparative effects of sulphonylurea and insulin treatment on glucose and lipid metabolism and insulin action have been the subject of a small number of studies. In mildly hyperglycaemic patients the effects of both treatments are comparable (35). However, insulin therapy is superior to sulphonylurea in patients who were more hyperglycaemic (36), as was demonstrated by us (chapter 6).

Sulphonylurea stimulate the release of endogenous insulin and probably improve peripheral insulin action (10). In patients, in whom intensified insulin treatment produces (near)normoglycaemia, an improvement of islet B-cell function and insulin action have been demonstrated (37-39). It has been argued that treatment with insulin results in considerable peripheral hyperinsulinaemia, thereby increasing the (theoretical) risk for developing atherosclerosis (40). In our studies, the average increase of fasting insulin levels approximated 40%. However, acceleration of diabetic complications due to (severe) hyperglycaemia in poorly controlled patients is of more relevance than the theoretical disadvantage of hyperinsulinaemia.

It is still difficult to assess which patients, who are poorly controlled by diet only, will benefit the most from insulin therapy. Our study suggests that by determination of C-peptide release after glucagon those patients can be identified in whom insulin therapy results in better blood glucose control than sulphonylurea (chapter 6).

When metabolic control is unsufficient with maximal doses of oral hypoglycaemic agents, insulin is the available option. It may be given alone, and substitute for the oral therapy, or be combined with sulphonylurea. A simple regimen comprising twice-daily administration of intermediate-acting or a mixture of fast- and intermediate-acting insulin significantly improves well-being and metabolic control with a slight concomitant improvement of plasma lipids.

Insulin therapy can be safely instituted on an outpatient base, which is an attractive possibility in a Health Care system facing large medical costs. No severe complications of insulin therapy are seen. Care must be taken to avoid hypoglycaemias (41). In patients, who do not attain adequate control with 2 injections, more intensive efforts are needed, for instance multiple injection regimens and instruction in self-regulation. Obesity does not seem to be a contraindication for institution of insulin treatment, when therapy with oral hypoglycaemic agents does not result in adequate control (11).

Although short-term studies have demonstrated a more favorable response of blood glucose control with combination of insulin and sulphonylurea in comparison to insulin alone (better metabolic control, lower insulin dose needed, less insulin injections), long term results are not yet available (42-44). Combined therapy is more expensive, and also more difficult for the patient. Our short-term results indicate a lower insulin need, when insulin treatment is added to existing therapy with glibenclamide, in comparison with insulin alone, while metabolic improvement was identical. Severe hypoglycaemias were not observed. In contrast to other findings (for review see 42) HDL-cholesterol levels equally increased with both treatment modalities. There is a tendency that patients with a higher residual insulin secretion respond more favorably, as is also demonstrated by other investigators (45). The long term results of combined therapy, especially with regards to changes of plasma cholesterol levels, have to be awaited.

On the basis of our findings the recommendations of the Dutch Standard of Care for General Practitioners need extension (26). These do not recognize the need for immediate insulin treatment, when blood glucose is severely deranged, while treatment steps (switching to oral agents or insulin) proceed rather slowly.

EDUCATION

Several factors are involved in the decision for elderly diabetic patients to start with insulin therapy, when blood glucose control has become inadequate despite diet and oral hypoglycaemic drugs (46). Many patients are reluctant to switch to insulin injections. Patients often do not perceive complaints, not even in the presence of severe hyperglycaemia, and therefore do not think that insulin treatment will improve their well-being (47). The study of Alogna (48) shows that type 2 diabetic patients, who are classified as compliant with treatment advices, rate their diabetes more severely than those classified as noncompliant. The perceived disadvantages of insulin therapy (painful, time-consuming, strict schedules and eating hours, stuck to home) may outweigh in the patient's point

of view the possible beneficial effects on glucose and lipid metabolism, and the patient may even be convinced that he or she is not capable to perform the difficult actions of injecting insulin (49). The main factor that explains the intention to commence insulin treatment appears to be the subjective norm. This means that patients are guided by the opinion of important other persons, in these circumstances especially the treating internist, and to a lesser extent the family physician and the diabetes nurse. Tablet-treated patients think that their physcician has a negative opinion towards their treatment with insulin. Intention to start insulin treatment is also determined by the determinant self-efficacy. This factor implies the patient's judgement of how well he can initiate and carry out the different tasks concerning injecting insulin. Self-monitoring of blood glucose with chemical strips and a higher knowledge about diabetes positively influence this self-efficacy, as well as the attitude towards and the intention to start insulin treatment. Earlier studies have already demonstrated that the quality of patient-provider relationships are an important factor in achieving adherence to medical advice (50). Inconsistent or one-sided communication from health-care professionals to patients results in incorrect representation of their illness and inhibits treatment adherence (51). These findings imply that education of type 2 diabetic patients, who are switching to insulin therapy, needs to enforce the subjective norm and improve the patient's self-efficacy. A stimulating and motivating attitude of the treating physician towards insulin therapy is essential.

FINAL REMARK

In conclusion, the occurrence of vascular abnormalities in patients with type 2 diabetes mellitus is high and their level of metabolic control usually is poor. Considering the apparent clustering of risk factors as poor metabolic control, obesity, hypertension and dyslipidaemia, attaining optimal blood glucose control forms only one of the aims of treatment in order to prevent the vascular complications, which severely limit the quality of life. Striving for normal blood glucose and HbA_{1c} levels seems futile without concomitant adequate treatment of elevated blood pressure and hypercholesterolaemia. To achieve these goals, proper education of the patients as well as their physicians is essential.

REFERENCES

1. DeFronzo RA. The triumvirate: beta-cell, muscle, liver: a collusion responsible for NIDDM. Diabetes 1988; 37: 667-687.
2. Efendic S, Luft R, Wajngot A. Aspects of the pathogenesis of type 2 diabetes. Endocrine Rev 1984; 5: 395-410.
3. Alberti KGMM, Gries FA. Management of non-insulin-dependent diabetes mellitus in Europe: a consensus view. Diabetic Med 1988; 5: 275-281.
4. Skyler JS. Non-insulin-dependent diabetes mellitus: a clinical strategy. Diabetes Care, 1984; 7 (suppl.1): 118-129.
5. Lipson LG, Lipson M. The therapeutic approach to the obese maturity-onset diabetic patient. Arch Intern Med 1984; 144: 135-138.
6. Schneider SH, Ruderman NB. Exercise and NIDDM. Technical Review. Diabetes Care 1990; 13: 785-789.
7. Wales JK. Treatment of type 2 (non-insulin-dependent) diabetic patients with diet alone. Diabetologia 1982; 23: 240-245.
8. Hadden DR, Montgomery DAD, Skelly RJ, et al. Maturity onset diabetes mellitus: response to intensive dietary management. Br Med J 1975; 2: 276-278.
9. Henry RR, Wallace P, Olefsky JM. Effects of weight loss on mechanisms of hyperglycemia in obese non-insulin-dependent diabetes mellitus. Diabetes 1986; 35: 990-998.
10. Gerich JE. Drug therapy-oral hypoglycemic agents. New Engl J Med 1989; 321: 1231-1245.
11. Heine RJ. Insulin treatment of non-insulin-dependent diabetes mellitus. In: Baillière's Clinical Endocrinology and Metabolism, Non-insulin-dependent diabetes. Nattrass M, Hale PJ, Eds. London, 1988.
12. Nathan DM, Singer DE, Godine JE, Perlmuter LC. Non-insulin-dependent diabetes in older patients-complications and risk factors. Am J Med 1986; 81: 837-842.
13. Fein FS, Scheuer J. Heart disease in diabetes. In: Ellenberg and Rifkin's Diabetes mellitus: Theory and Practice. Rifkin H, Porte D Jr, Eds. 4th Edition, New Hyde Park, NY, Elsevier Science Publishing Co, 1990.
14. Jarrett RJ. Epidemiology and public health aspects of non-insulin-dependent diabetes mellitus. Epidemiol Rev 1989; 11: 151-171.
15. Levin ME, Sicard GA. Peripheral vascular disease in the person with diabetes. In: Ellenberg and Rifkin's Diabetes mellitus: Theory and Practice. Rifkin H, Porte D Jr, Eds. 4th Edition, New Hyde Park, NY, Elsevier Science Publishing Co 1990.
16. Drury PL. Non-insulin-dependent diabetes and hypertension. In: Baillière's Clinical Endocrinology and Metabolism, Non-insulin-dependent diabetes. Nattrass M, Hale PJ, Eds. London, 1988.
17. Betteridge DJ. Lipids, diabetes and vascular disease: the time to act. Diabetic Med 1989; 6: 195-218.
18. Verhoeven S. Treatment, follow-up and metabolic regulation of patients with diabetes mellitus type II and the prevalence of late complications in this group of patients. Thesis, Rotterdam/Heerde, 1989.
19. Allawi J, Jarrett RJ. Microalbuminuria and cardiovascular risk factors in type 2 diabetes mellitus. Diabetic Med 1989; 7: 115-118.

20. Marshall SM, Alberti KGMM. Comparison of the prevalence and associated features of abnormal albumin excretion in insulin-dependent and non-insulin-dependent diabetes. Q J Med 1989; 70: 61-71.
21. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. New Engl J Med 1984; 310: 356-360.
22. Jarrett RJ, Viberti GC, Argyropoulos A, Hill RD, Mahmud U, Murells T. Microalbuminuria predicts mortality in non-insulin-dependent diabetes. Diabetic Med 1984; 1: 17.
23. Assmann G, Schulte H. Diabetes mellitus and hypertension in the elderly: concomitant hyperlipidemia and coronary heart disease risk. Am J Cardiol 1989; 63: 33H-37H.
24. Rosengren A, Welin L, Tsipogianni A, Wilhelmsen L. Impact of cardiovascular risk factors on coronary heart disease and mortality among middle aged diabetic men: a general population study. Br Med J 1989; 299: 1127-1131.
25. Mooradian AD, Osterweil D, Petrasek D, Morley JE. Diabetes mellitus in elderly nursing home patients. A survey of clinical characteristics and management. J Am Geriatr Soc 1988; 36: 391-396.
26. Rutten GEHM, Cromme PVM, Zuidweg J, Mulder Dzn JD. The general practitioner and diabetes type II. A justification for the NHG standard. Huisarts Wet 1989; 32: 7-13.
27. Holman RR, Turner RC. Optimizing blood glucose control in type 2 diabetes: an approach based on fasting blood glucose measurements. Diabetic Med 1988; 5: 582-588.
28. Winocour PH, Bhatnagar D, Kalsi P, Hillier VF, Anderson DC. An analysis of glycosylated blood proteins and blood glucose profiles over one year in patients with type 1 diabetes. Diabetic Med 1989; 6: 709-716.
29. Howey JEA, Bennet WM, Browning MCK, Jung RT, Fraser CG. Clinical utility of assays of glycosylated heamoglobin and serum fructosamine compared: use of data on biological variation. Diabetic Med 1989; 6: 793-796.
30. Larsen ML, Horder M. Metabolic evaluation of non-insulin-dependent diabetes in primary health care the clinical usefulness of glycated haemoglobin measurements. Scand J Prim Health Care 1989; 7: 167-171.
31. Johnson RN, Metcalf PA, Baker JR. Fructosamine: a new approach to the estimation of serum glycosylprotein. An index of diabetic control. Clin Chim Acta 1982; 127: 87-95.
32. Armbuster DA. Fructosamine: structure, analysis and clinical usefulness. Clin Chem 1987; 33: 2153-2163.
33. Hughes TA, Gwynne JT, Switzer BR, Herbst C, White G. Effects of caloric restriction and weight loss on glycemic control, insulin release and resistance, and atherosclerotic risk in obese patients with type II diabetes mellitus. Am J Med 1984; 77: 7-17.
34. Uusitupa MIJ, Laakso M, Sarlund H, Majander H, Takala J, Penttilä I. Effects of a very-low-calorie diet on metabolic control and cardiovascular risk factors in the treatment of obese non-insulin-dependent diabetics. Am J Clin Nutr 1990; 51: 768-773.
35. Firth RG, Bell PM, Rizza RA. Effects of tolazamide and exogenous insulin on insulin action in patients with non-insulin-dependent diabetes mellitus. New Engl J Med 1986; 314: 1280-1286.
36. Samanta A, Burden AC, Kinghorn A. A comparative study of sulphonylurea and insulin therapy in non-insulin-dependent diabetics who had failed on diet therapy. Diabetes Res 1987; 4: 183-185.

37. Glaser B, Leibovich G, Nesher R, Hartling S, Binder C, Cerasi E. Improved beta-cell function after intensive insulin treatment in severe non-insulin-dependent diabetes. Acta Endocrinol 1988; 118: 365-373.
38. Garvey WT, Olefsky JM, Griffin J, Hamman RF, Kolterman OG. The effect of insulin treatment on insulin secretion and insulin action in type II diabetes mellitus. Diabetes 1985; 34: 222-234.
39. Ginsberg H, Rayfield EJ. Effect of insulin therapy on insulin resistance in type II diabetic subjects-evidence for heterogeneity. Diabetes 1981; 30: 739-745.
40. Stout RW. The role of insulin in atherosclerosis in diabetics and nondiabetics. Diabetes 1981; 30 (suppl 2): 54-57.
41. Nilsson A, Tideholm B, Kalen J, Katzman P. Incidence of severe hypoglycemia and its causes in insulin-treated diabetics. Acta Med Scand 1988; 224: 257-262.
42. Wolffenbuttel BHR. Combined use of insulin and oral hypoglycaemic agents in the treatment of patients with diabetes mellitus. Eur J Intern Med 1989; 1: 89-95.
43. Bailey TS, Mezitis NHE. Combination therapy with insulin and sulfonylureas for type II diabetes. Diabetes Care 1990; 13: 687-695.
44. Lebovitz HE, Pasmantier R. Combination insulin-sulfonylurea therapy. Diabetes Care 1990; 13: 667-675.
45. Castillo M, Scheen AJ, Paolisso G, Lefebvre PJ. The addition of glipizide to insulin therapy in type II diabetic patients with secondary failure to sulfonylureas is useful only in the presence of a significant residual insulin secretion. Acta Endocrinol 1987; 116: 364-372.
46. Tattersall RB, Scott AR. When to use insulin in the maturity onset diabetic. Postgrad Med J 1987; 63: 859-864.
47. Tattersall RB. Diabetes in the elderly; a neglected area? Diabetologia 1974; 27: 167-173.
48. Alogna M. Perception of severity of disease and health locus of control in compliant and noncompliant diabetic patients. Diabetes Care 1980; 3: 533-534.
49. Jacobsen AM, Hauser ST. Behavioural and psychological aspects of diabetes. In Diabetes mellitus: Theory and Practice. 3rd Ed. Ellenberg M, Rifkin H, Eds. New Hyde Park, NY, Elsevier Publishing Co, 1983.
50. Roter DL, Hall JA, Katz NR. Patient-physician communication: a descriptive summary of the literature. Patient Education and Counselling 1988; 12: 99-119.
51. Anderson LA, Halter JB. Diabetes care in older adults: current issues in management and research. In: Geriatric Health Issues, p.35-73.

CHAPTER 11

Summary

This thesis deals with the spectrum of secondary complications, that occur in patients with type 2 diabetes mellitus, and the effects of dietary and insulin treatment on glucose and lipid metabolism in these patients.

Chapter 1 gives an overview of the pathophysiologic mechanisms leading to hyperglycaemia and responsible for the development of late complications in persons with type 2 diabetes mellitus. A summary is given of the current insights in treatment of diabetes and the ways to achieve near-normal blood glucose control, and emphasizes the importance of other risk factors for the development of cardiovascular disease.

In chapter 2 the results of a survey among patients treated at the outpatient clinic of the Department of Internal Medicine of the University Hospital Maastricht are described. This study was performed in order to attain more information on the quality of metabolic control and presence of secondary complications in these patients. The presence of diabetic complications was assessed by specific questionnaires and detailed physical examination, and compared with a recently published survey among G.P. patients. As expected a higher proportion of our patients was treated with insulin (48% *vs.* 24%, $p<0.01$). In addition, they showed a higher prevalence of hypertension (56% *vs.* 38%), coronary artery disease (48% *vs.* 40), and cerebrovascular disease (15% *vs.* 6%). 35% of our patients had signs of peripheral artery disease. Retinopathy was present in 35 patients (28%), of whom 18 had received lasercoagulation treatment. Microalbuminuria was found in 25%, and overt proteinuria in 14% of patients. The presence of microalbuminuria and proteinuria was a strong indicator for cardiovascular disease, polyneuropathy and retinopathy. The use of cardiovascular medication was high: 57 patients used antihypertensive therapy, 37 used diuretics, and 26 long-acting nitrates. Only 25 patients took no medication in addition to their diabetes therapy. This study confirms the clustering of risk factors for cardiovascular disease in type 2 diabetes mellitus.

Chapter 3 describes the clinical situation and presence of secondary diabetic complications of 38 diabetic patients, chronically admitted to a nursing home. Their macrovascular complications and degree of glycaemic control were compared with those in ambulatory diabetic patients, matched for age, sex, known duration of diabetes, and specific antidiabetic therapy. No differences in blood glucose control, plasma triglycerides, blood pressure and serum creatinine were observed between both groups of patients, although plasma cholesterol levels were higher in the ambulatory patients. A high prevalence of cerebrovascular disease, peripheral vascular abnormalities, skin necrosis or leg ulcers and recurrent urinary tract infections was found in the nursing home patients. Hypertension was found in almost 50% of all patients, whereas its prevalence was the highest in the stroke patients. In the ambulatory patients cardiac complaints were more prevalent. Use of medication, especially diuretics and anticoagulant agents, was higher in the nursing home patients.

In chapter 4 the value of fasting blood glucose and serum fructosamine to reliably predict glycaemic control as measured by HbA_{1c} (HPLC-method) was assessed in 264 type 2 diabetic patients on various treatments. Correlation between fasting blood glucose and HbA_{1c} was slighly lower ($r=0.67$ for all patients ($p<0.001$)). This was higher in patients on diet ($r=0.75$), compared to patients treated with sulphonylurea ($r=0.70$), insulin ($r=0.59$) and insulin + sulphonylurea ($r=0.52$). Correlation between fasting blood glucose and serum fructosamine was, although significant, even weaker. The within-subject correlations between the three glycaemic measures were considerably lower. A fasting blood glucose level <8.0 mmol/l correctly predicted HbA_{1c} below 7.5% in only 64% of cases. There was a clear circadian variation of serum fructosamine, as assessed in 15 hospitalized patients. Thus, a normal fasting blood glucose level is a poor predictor of long term adequate glycaemic control as assessed by HbA_{1c}. Serum fructosamine determinations show considerable variation, and have no clinical advantage over HbA_{1c} measurements.

Chapter 5 describes a study of intensified dietary treatment in sixty-one ambulatory patients with type 2 diabetes mellitus and fasting blood glucose levels above 7 mmol/l (average 12.0 ± 0.6 mmol/l). At the start of the study 33 patients were obese. Non-obese patients showed more severe beta-cell deficiency than obese, and did not improve in blood glucose control during diet. In the obese patients three response patterns to treatment were observed: weight loss and improvement in metabolic control accompanied primarily with increased beta-cell function or increased insulin action, or worsening of metabolic control. Those with less impaired beta-cell function and shorter known duration

of diabetes showed the most favourable response. Weight reduction was essential to obtain metabolic improvement, irrespective of the preceeding fasting blood glucose concentrations.

Chapter 6 describes the effects of 6 months insulin or sulphonylurea therapy on blood glucose control and lipid metabolism in a randomized crossover study in 13 non-obese patients with type 2 diabetes mellitus who failed to achieve adequate blood glucose control on dietary treatment. Three patients, who showed a clear improvement on insulin (median glycosylated haemoglobin fell from 14.7 to 8.6%), withdrew from the study prematurely because of subjective and objective signs of hyperglycaemia after crossover from insulin to sulphonylurea, thus favoring the insulin treatment. In the other 10 patients, fasting and postprandial blood glucose levels, and glycosylated haemoglobin were lower during insulin than on sulphonylurea. Increase in body weight was somewhat greater on insulin therapy. Six patients experienced improved well-being on insulin compared with sulphonylurea. A significantly higher HDL-cholesterol level was found after insulin treatment than after sulphonylurea, whereas the LDL:HDL-cholesterol ratio and VLDL-triglycerides were lower. On the basis of C-peptide response after intravenous injection of glucagon those patients could be identified, who had better blood glucose control with insulin.

In chapter 7 it was shown that a simple regimen comprising twice-daily administration of intermediate-acting or a mixture of fast- and intermediate-acting insulin significantly improved blood glucose control with a slight concomitant improvement of plasma lipids. This improvement of blood glucose control in the individual patient was directly correlated with the increase in body weight, that was observed in these patients. This implies that more severe hyperglycaemia reflects a more catabolic state, which is reversed by insulin therapy. Insulin therapy could be safely instituted on an outpatient base. Almost all patients reported improved well-being, and disappearance of hyperglycaemic symptoms. Such symptoms often were previously not recognized as such. No severe complications of insulin therapy were seen. In the obese patients a comparable improvement in blood glucose control was achieved. Thus, obesity does not seem to be a contraindication for institution of insulin treatment.

In chapter 8 the possible advantages of more complicated treatment regimens, involving a combination of insulin and sulphonylurea was reported in type 2 diabetic patients with secondary failure to oral hypoglycaemic agents. A scheme comprising twice-daily insulin injections was compared with regimens of once-daily insulin in combination with glibenclamide. With both treatment regimens patients reported improved well-being and diminished hyperglycaemic complaints, while no severe hypoglycaemias were observed. The increase

in body weight, and improvement of blood glucose control was comparable with all treatments. However, with combined therapy insulin dose was lower (26 *vs.* 42 U). With both treatments significant increases of HDL-cholesterol were observed, while plasma triglycerides and non-esterified fatty acids decreased. Total cholesterol decreased only in the patients treated with insulin alone. Apolipoproteins AI, AII and B did not show any significant changes. The increase of HDL-cholesterol without concomitant increase of apolipoproteins AI and AII suggest enrichment of the HDL-particle with cholesterol during insulin therapy.

Chapter 9 describes the factors which determine the decision for elderly diabetic patients to start with insulin therapy, when blood glucose control has become inadequate despite diet and oral hypoglycaemic drugs. According to Fishbein and Ajzen an attitude-behaviour model was constructed which included the determinants intention, attitude, subjective norm and self-efficacy. A high correlation existed between the intention to and the actual start or continuation of insulin therapy. The main factor that explained the intention to commence insulin treatment was the subjective norm. This means that patients are guided by the opinion of important other persons, in these circumstances especially the treating internist, the family physician and the diabetes nurse. Tablet-treated patients reported a negative opinion of their physician towards their treatment with insulin. Intention was also determined by self-efficacy, e.g. expectations about the skills concerning injecting insulin. Self-monitoring of blood glucose and knowledge about diabetes positively influenced self-efficacy, attitude towards and intention to start insulin treatment. These findings imply that education needs to enforce the subjective norm and improve the patient's self-efficacy, and that a stimulating attitude of the treating physician towards insulin therapy is essential.

CHAPTER 12

Samenvatting

Dit proefschrift exploreert het spectrum van de late complicaties, die kunnen ontstaan bij personen met diabetes mellitus type 2, en beoordeelt de effecten van dieet- en insuline-therapie op glucose- en vetstofwisseling bij deze patiënten.

Hoofdstuk 1 geeft een overzicht van de pathofysiologische mechanismen, die leiden tot de hyperglycemie, en verantwoordelijk zijn voor het ontstaan van late complicaties bij personen met diabetes mellitus type 2. De huidige inzichten in de behandeling van diabetes, de manieren waarop bijna-normale bloedglucose-regulatie kan worden bereikt, en het belang van andere risicofactoren bij het ontwikkelen van hart- en vaatziekten worden besproken.

In hoofdstuk 2 worden de resultaten beschreven van een onderzoek naar de kwaliteit van metabole instelling en aanwezigheid van secundaire complicaties bij een aselecte steekproef van type 2 diabetes patiënten, die op de polikliniek van de afdeling Inwendige Geneeskunde worden behandeld. De aanwezigheid van complicaties werd vergeleken met de resultaten van een recent gepubliceerd inventarisatie-onderzoek onder patiënten in een huisartsenpraktijk. Naar verwachting bleek een groter aantal van onze patiënten met insuline te worden behandeld (48% *vs.* 24%, $p<0.01$). Tevens bleek er een hogere prevalentie te bestaan van hypertensie (56% *vs.* 38%), coronairlijden (48% *vs.* 40%), en cerebrovasculaire afwijkingen (15% *vs.* 6%). 35% van onze patiënten had tekenen van perifeer vaatlijden, terwijl retinopathie aanwezig was bij 35 patiënten (28%); 18 van hen waren reeds met lasercoagulatie behandeld. Microalbuminurie werd geconstateerd bij 25%, en manifeste proteinurie bij 14% der patiënten. De aanwezigheid van microalbuminurie en proteinurie bleek een goede indicator voor de aanwezigheid van cardiovasculaire afwijkingen, polyneuropathie en retinopathie. Het gebruik van cardiovasculaire medicatie was aanzienlijk: 57 patiënten gebruikten bloeddrukverlagende medicijnen, 37 gebruikten diuretica, en 26 lang-werkende nitraten. Slechts 25 patiënten gebruikten geen medicijnen naast hun specifieke antidiabetische behandeling. Dit

onderzoek bevestigt de clustering van risicofactoren voor hart- en vaatziekten bij patiënten met type 2 diabetes mellitus.

Hoofdstuk 3 beschrijft de metabole regulatie en aanwezigheid van secundaire complicaties bij 38 diabetes patiënten, die chronisch opgenomen waren in 2 Maastrichtse verpleegklinieken. De resultaten werden vergeleken met bevindingen bij een voor wat betreft leeftijd, geslacht, bekende duur van de diabetes en antidiabetische therapie vergelijkbare groep poliklinisch behandelde patiënten. De door ons onderzochte patiënten betroffen 15% van de populatie van de betrokken verpleeghuizen. Tussen beide groepen werden geen verschillen in diabetes instelling, plasma triglyceriden, bloeddruk en nierfunctie gevonden. De plasma cholesterolgehalten van de poliklinische patiënten waren hoger. 22 van de patiënten in de verpleegkliniek hadden een cerebrovasculair accident (CVA) doorgemaakt, tegen 4 poliklinische patiënten. Bij 18 van deze 22 patiënten had het CVA geleid tot hemiparese en verzorgingsbehoefte, en was dit de reden voor opname in de verpleegkliniek geweest. De prevalentie van hypertensie bedroeg 50%, waarbij hypertensie frequenter voorkwam bij de CVA-patiënten, in vergelijking met de patiënten zonder cerebrovasculaire aandoeningen. De verpleegkliniek-patiënten hadden een hoge frequentie van perifeer vaatlijden (76%) en amputaties (24%), huidnecrose en ulcera cruris, en urineweginfecties (76%), terwijl bij de poliklinisch behandelde patiënten cardiale klachten frequenter voorkwamen (47% *vs.* 24%, $p<0.01$). Medicatie-gebruik, met name van diuretica en antistollingsmiddelen, was hoger bij de verpleegkliniek-patiënten.

In hoofdstuk 4 wordt de waarde van het nuchtere bloedglucose en serum fructosamine gehalte beoordeeld om de kwaliteit van metabole controle te voorspellen. Een met de HPLC-methode bepaalde concentratie van geglycosyleerd hemoglobine is hierbij de 'gouden standaard'. In totaal werden 264 patiënten bestudeerd. De correlatie tussen nuchter bloedglucose en HbA_{1c} was iets lager ($r=0.67$ voor alle patiënten ($p<0.001$)). Deze correlatie was het grootst bij met dieet behandelde patiënten ($r=0.75$), in vergelijking met patiënten, die met tabletten ($r=0.70$), insuline ($r=0.59$) of insuline + sulfonylurea ($r=0.52$) werden behandeld. De correlatie tussen nuchter bloedglucose en serum fructosamine was nog lager. De correlatie tussen de drie variabelen van glycemische controle binnen één persoon waren aanzienlijk lager. Een nuchter bloedglucose gehalte <8.0 mmol/l voorspelde een HbA_{1c} lager dan 7.5% slechts correct in 64% van de gevallen. Er bestond een duidelijke variatie van het serum fructosamine gehalte gedurende de dag, met een significante postprandiale stijging om 10 uur 's ochtends. Het nuchtere bloedglucose gehalte heeft een matige voorspellende waarde voor het HbA_{1c} gehalte. Het serum fructosamine vertoont

gedurende de dag aanzienlijke variatie, en heeft geen voordelen boven de bepaling van het geglycosyleerd hemoglobine.

Hoofdstuk 5 beschrijft een onderzoek naar de effecten van intensieve dieet therapie bij 61 ambulante patiënten met type 2 diabetes mellitus met een nuchter bloedglucose-gehalte hoger dan 7.0 mmol/l (gemiddeld 12.0 ± 0.6 mmol/l). Bij aanvang van het onderzoek hadden 33 patiënten een overgewicht. Niet-obese patiënten toonden een ernstiger defect in insuline-secretie dan obese patiënten. Tijdens dieet verbeterde hun glucose-regulatie niet. Bij de patiënten met overgewicht werden drie vormen van respons waargenomen: gewichtsverlies met verbetering van de metabole regulatie bij een verbetering van de residuele insuline-secretie dan wel een verbetering van de insuline-werking, of verslechtering van de glucose-regulatie. Diabeten met een hogere residuele insuline-secretie of met een korte duur van de diabetes toonden de meest gunstige respons. Gewichtsverlies was essentieel om een verbetering van de instelling te bereiken, onafhankelijk van de hoogte van het bloedglucose-gehalte.

In hoofdstuk 6 worden de effecten op glucose- en vetstofwisseling van 6 maanden behandeling met insuline vergeleken met sulfonylurea therapie in een gerandomizeerde cross-over studie bij 13 type 2 diabetes patiënten met een normaal lichaamsgewicht, die met dieet alleen niet goed gereguleerd waren. Drie patiënten vielen voortijdig uit de studie, vanwege hyperglycemische klachten nadat zij van insuline overgegaan waren naar tablet therapie. Zij toonden een sterke verbetering van metabole regulatie tijdens insuline, waarbij de mediane waarde van het geglycosyleerd hemoglobine daalde van 14.7 naar 8.6%. Bij de overige 10 patiënten waren de nuchtere en postprandiale bloedglucose spiegels, en het geglycosyleerd hemoglobine lager gedurende insuline in vergelijking met tablet therapie. De toename van het lichaamsgewicht was tijdens insuline echter groter. Zes patiënten rapporteerden dat zij zich tijdens insuline therapie beter voelden dan tijdens tablet behandeling. Tijdens insuline was het HDL-cholesterol gehalte significant hoger, en de LDL:HDL-cholesterol ratio en het VLDL-triglyceriden gehalte waren lager. Op basis van de stijging van het plasma C-peptide gehalte na injectie van 1 mg glucagon konden die patiënten worden geidentificeerd, die tijdens insuline beter gereguleerd waren.

In hoofdstuk 7 wordt aangetoond dat een eenvoudig insuline schema met tweemaal daagse toediening van middellangwerkend insuline of een mengsel van middellangwerkende en snelwerkende insuline de diabetes instelling sterk verbeterde bij personen met falen op orale therapie. Er bleek een duidelijke relatie tussen de metabole verbetering en de toename van het lichaamsgewicht. Bij de meeste patiënten werd zonder problemen de insuline behandeling poliklinisch aangevangen. Bijna alle patiënten meldden een verbetering van het welbevinden, en een vermindering van, vaak niet tevoren als zodanig herkende,

hyperglycemische klachten. Aangezien de 6 patiënten met overgewicht een vergelijkbare verbetering van de diabetes instelling toonden, is obesitas ons inziens geen reden om insuline behandeling achterwege te laten.

In hoofdstuk 8 worden de metabole effecten van combinatie van insuline met glibenclamide bestudeerd bij patiënten met secundair falen op orale therapie. Zowel met insuline alleen als met combinatie-therapie verbeterde het welbevinden van de patiënten en verdwenen hyperglycemische klachten; ernstige hypoglycemieën werden niet waargenomen. Er was bij beide behandelingsschema's een vergelijkbare toename van het lichaamsgewicht en daling van de bloedglucosegehalten. Echter, bij combinatie-therapie was de benodigde dosis insuline lager (26 *vs.* 42 E). Een significante stijging van het HDL-cholesterol, en daling van vrije vetzuren en triglyceriden werd waargenomen. Het totale cholesterolgehalte daalde alleen bij patiënten, die insuline gebruikten. Het gehalte van de apolipoproteinen AI, AII en B veranderde niet. De toename van het HDL-cholesterol zonder stijging van het apoAI gehalte betekent een verrijking van het HDL-partikel met cholesterol onder invloed van insuline.

In hoofdstuk 9 worden de factoren bestudeerd die de beslissing van een persoon met diabetes om insuline te gaan spuiten beinvloeden. Naar het model van Fishbein and Ajzen werd een attitude-gedrag model opgesteld, dat de determinanten intentie, attitude, subjectieve norm en self-efficacy omvatte. Er bestond een hoge correlatie tussen de intentie om insuline te gaan of blijven spuiten en het daadwerkelijk vertonen van dit gedrag. De belangrijkste factor die deze intentie bepaalde was de subjectieve norm. Dit betekent dat patiënten in aanzienlijke mate geleid worden door zgn. belangrijke andere personen, in dit geval de behandelend specialist, de huisarts, en de diabetesverpleegkundige. Patiënten die tabletten gebruikten rapporteerden een negatieve houding van hun behandelend arts ten aanzien van insuline therapie. De intentie werd tevens bepaald door de self-efficacy, dat wil zeggen de mate waarin een individu verwacht om technisch moeilijke handelingen (prikken, juiste hoeveelheid insuline bepalen) goed te kunnen uitvoeren. Het zelf kunnen bepalen van het bloedglucosegehalte en kennis omtrent diabetes beinvloedden de self-efficacy, attitude en intentie positief. Educatie dient derhalve de subjectieve norm te versterken en de self-efficacy van een patiënt te verbeteren. Een stimulerende houding van de behandelende arts ten aanzien van insuline behandeling is essentieel.

CHAPTER 13

Evaluation and treatment of patients with type 2 diabetes

Practical guidelines

Table 1. Instruction, treatment and follow-up of the type 2 diabetic patient.

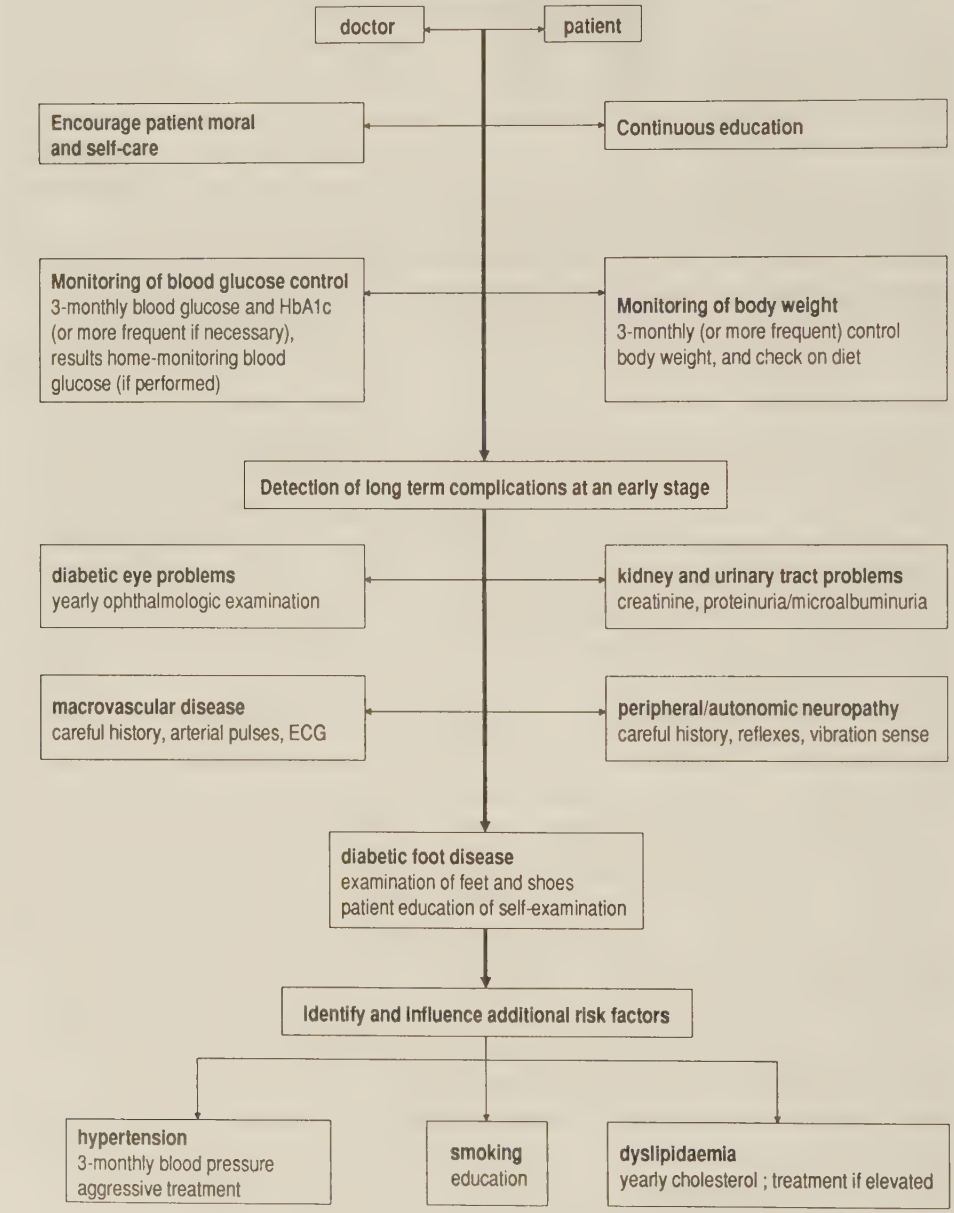
doctor
patient
Encourage patient moral and self-care
Continuous education
Monitoring of blood glucose control
3-monthly blood glucose and HbA1c (or more frequent if necessary), results home-monitoring blood glucose (if performed)
Monitoring of body weight
3-monthly (or more frequent) control body weight, and check on diet
Detection of long term complications at an early stage
diabetic eye problems
yearly ophthalmologic examination
kidney and urinary tract problems
creatinine, proteinuria/microalbuminuria
macrovascular disease
careful history, arterial pulses, ECG
peripheral/autonomic neuropathy
careful history, reflexes, vibration sense
diabetic foot disease
examination of feet and shoes
patient education of self-examination
Identify and influence additional risk factors
hypertension
3-monthly blood pressure
aggressive treatment
smoking
education
dyslipidaemia
yearly cholesterol ; treatment if elevated

Table 2. Check-up in a patient with type 2 diabetes mellitus.

First visit:
Careful and extensive history
General physical examination
Body weight, blood pressure supine and standing
Fundoscopy + visual acuity (ophthalmologist)
Specific examination for neuropathy
Foot inspection
Fasting and postprandial blood glucose
HbA_{1c}
Cholesterol, triglycerides, HDL-cholesterol
Urine protein, microalbuminuria, ketone bodies
Urine microscopy and culture
Plasma creatinine
ECG
Dietary advice (dietician)
Advice for regular physical exercise
Start education
Self monitoring of blood glucose?
Monthly: (when control is poor or insulin treatment)
Body weight
Fasting (and postprandial?) blood glucose
Continue education
Once every three months:
As monthly, plus:
Blood pressure
HbA_{1c}
Lipids, when elevated at a prior determination, or treated
Yearly:
Metabolic and physical examination as with first visit
Examination for late complications, including ophthalmologic investigation

Table 3. Annual review of type 2 diabetic patients.

HISTORY		PHYSICAL EXAMINATION
diabetes regulation: hypoglycaemic episodes hyperglycaemic complaints changes in body weight		
changes in vision		ophthalmological examination: visual acuity, fundoscopy, cataract
smoking dietary adherence drug or insulin administration other medication		
vascular symptoms: chest pain, on exertion or in rest claudication, rest pain		blood pressure (supine and standing) arterial pulses body weight
genitourinary symptoms pruritus vulvae sexual disturbances		injection sites
neurological symptoms		neurologic examination
complaints of feet		foot and shoes examination

Table 4. Monitoring of treatment targets and cardiovascular risk factors in patients with type 2 diabetes mellitus.

	Good	Fair	Poor
Body mass index (kg/m^2)			
males	22 - 25	25 - 27	> 27
females	22 - 24	24 - 26	> 26
Blood glucose (mmol/l)[1]			
fasting	4.4 - 6.7	6.7 - 8.0	> 8.0
post-prandial	4.4 - 9.0	9.0 - 12.0	> 12.0
HbA_{1c} (%)	< 7.5	7.5 - 9.0	> 9.0
Total cholesterol (mmol/l)	< 5.2	5.2 - 6.5	> 6.5
HDL-cholesterol (mmol/l)	> 1.1	0.9 - 1.1	< 0.9
Triglycerides (mmol/l)	< 1.7	1.7 - 2.2	> 2.2
Blood pressure (mm Hg)			
systolic	< 140	140 - 160	> 160
diastolic	< 85	85 - 100	> 100
Microalbuminuria 24-hour urine (mg/24h)	< 30		
early morning sample albumin/creatinin ratio	< 3.0		
Cigarette smoking	0		

[1] dependent on age and therapy goal

After: Alberti KGMM, Gries FA. Management of non-insulin-dependent diabetes mellitus in Europe: a consensus view. Diabetic Med 1988; 5: 275-281.

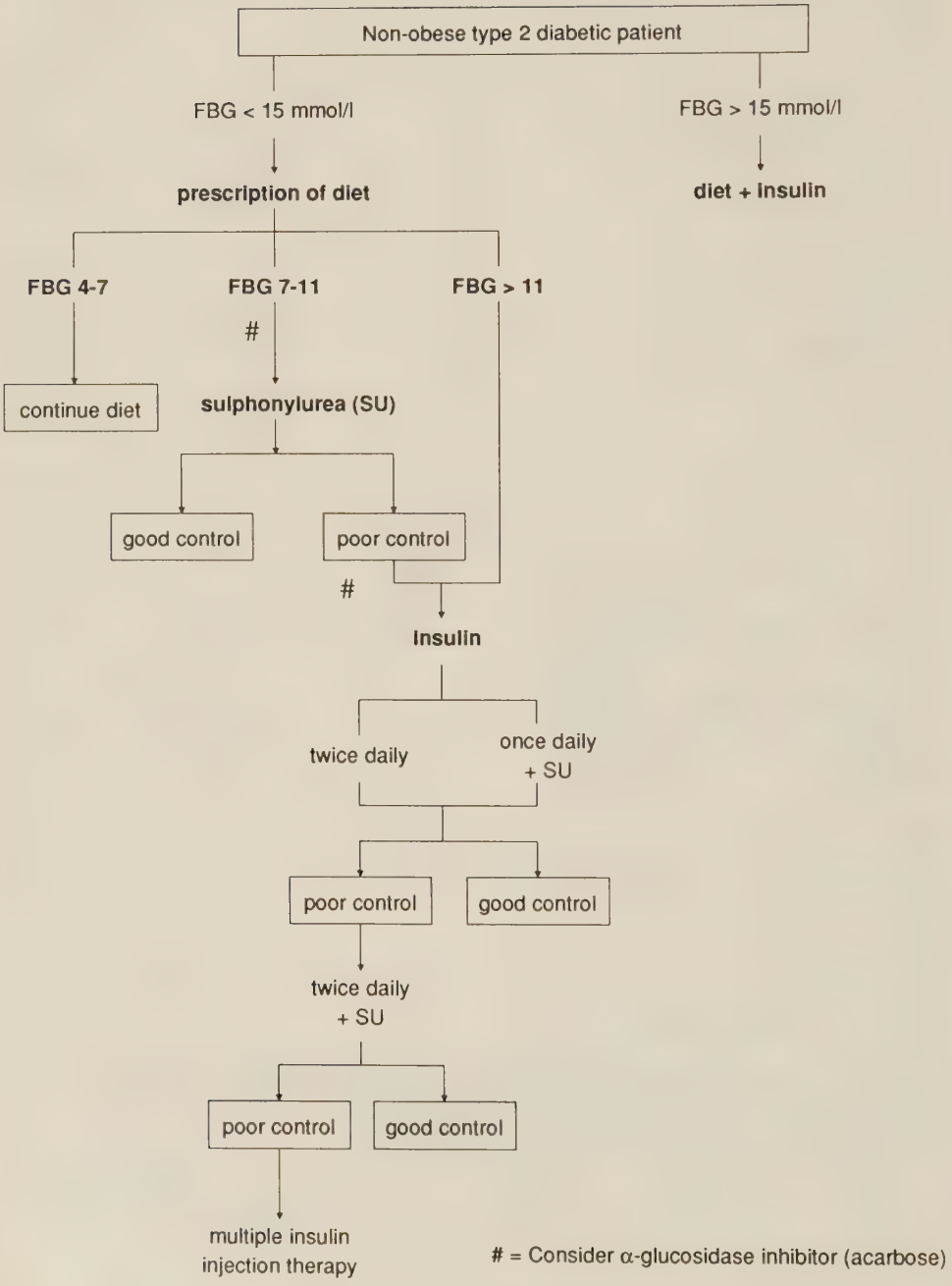

Fig 1. Treatment of type 2 diabetes mellitus: non-obese patients.

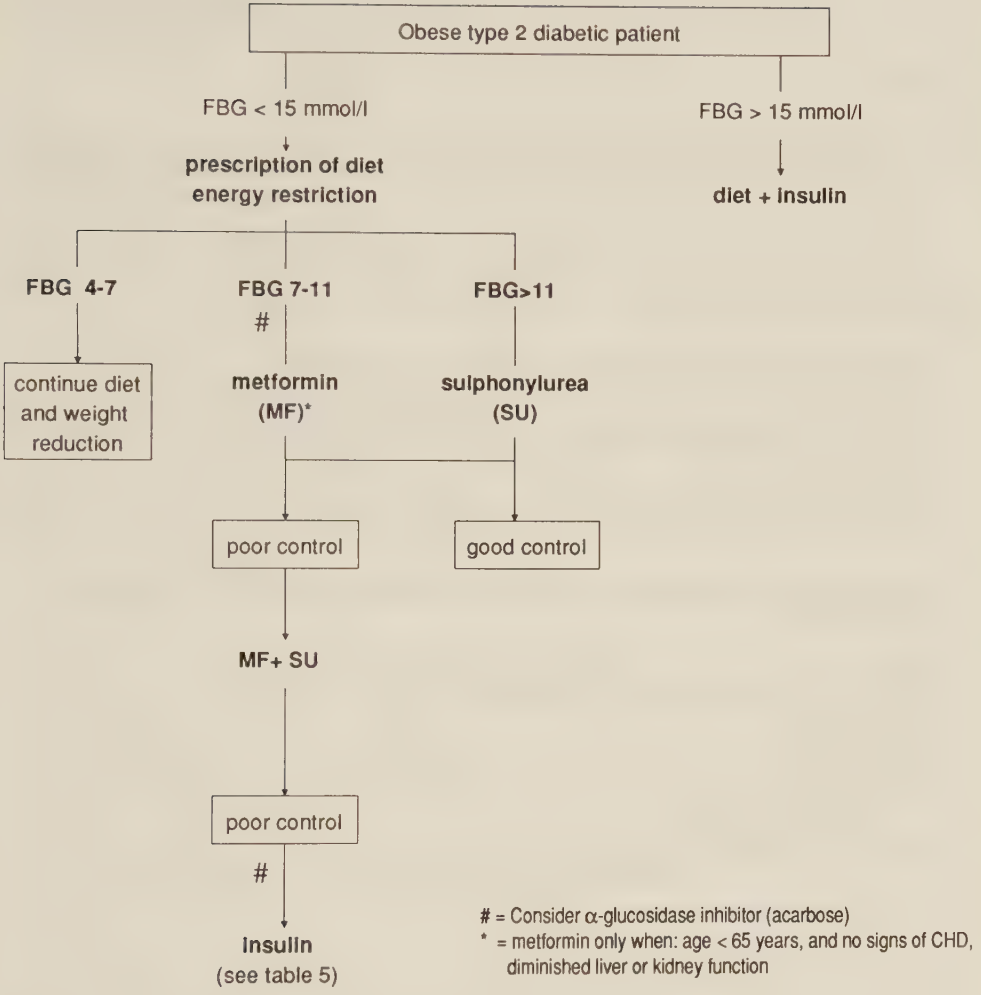

Fig 2. Treatment of type 2 diabetes mellitus: obese patients.

Table 5. Institution of insulin therapy in type 2 diabetes mellitus.

1. Insulin administration preferrably by means of an insulin-pen.

2. Out-patient institution of insulin therapy can be achieved only with proper instruction and motivation of the patient, and by preference when self-monitoring of blood glucose is possible.

   When a patient is not capable to inject insulin him/herself, then assistance of registered nurses is essential.

3. Use an insulin administration scheme which is as easy as possible:
   for instance:
   twice-daily administration (before breakfast and supper) of a mixture of fast-acting and NPH-insulin.
   or
   once-daily injection of an insulin mixture in combination with glibenclamide before meals.

4. Adjust the amount of insulin in relation to the blood glucose determinations which are made by the patient.

5. Regularly check the most important variables:
   - body weight
   - blood glucose measurements
   - insulin injection sites
   - insulin injection technique
   - possible hypoglycaemias

Nawoord

Onderzoek als in dit proefschrift beschreven zou niet mogelijk geweest zijn zonder de hulp van zeer velen.
De welwillende en enthousiaste medewerking van alle patiënten was cruciaal.

Prof. dr. A.C. Nieuwenhuijzen Kruseman kent naast een kritisch oog en oor ook de gave om medewerkers zelfstandig, en toch solide gesteund, wetenschap te laten beoefenen.

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Susanne, Alain en Francien maakten het allemaal echt mogelijk.

Curriculum vitae

De schrijver van dit proefschrift werd geboren op 19 september 1955 in het hart van Rotterdam. Na het behalen van het Gymnasium ß diploma aan het Gymnasium Erasmianum te Rotterdam werd in 1973 met de studie Geneeskunde aangevangen aan de tegenover dit gymnasium gelegen Medische Faculteit van de Erasmus Universiteit. Tijdens de studie is als keuze-praktikant en aansluitend als student-assistent onderzoek gedaan op het Laboratorium voor Experimentele Cardiologie van het Thoraxcentrum (hoofd: prof. dr. P.D. Verdouw). In 1980 werd het artsexamen afgelegd. In 1981 was hij werkzaam als arts-assistent Inwendige Geneeskunde in het Ikazia Ziekenhuis te Rotterdam. Het jaar 1982 werd wederom doorgebracht op de afdeling Experimentele Cardiologie, alwaar onderzoek werd verricht naar de effecten van calcium-antagonisten en bèta-blokkers op regionale myocardischemie. Hij volgde zijn opleiding tot internist in de afdeling Inwendige Geneeskunde III van het Academisch Ziekenhuis Rotterdam - "Dijkzigt" (opleider: prof. dr. J.C. Birkenhäger), alwaar hij aan een deel van het beschreven onderzoek heeft gewerkt. Vanaf 1 januari 1988 is hij geregistreerd als internist, en werkzaam in de werkgroep Endocrinologie (prof. dr. A.C. Nieuwenhuijzen Kruseman) van de afdeling Inwendige Geneeskunde (hoofd: prof. dr. J.A. Flendrig) van het Academisch Ziekenhuis Maastricht, alwaar het vervolgonderzoek plaats vond, en dit proefschrift werd afgerond.